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PULMONARY EMBOLISM

A REPORT OF SEVENTY-THREE CASES *

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This report is based on seventy-three cases of fatal pulmonary embolism, from the records of the Department of Pathology of the University of Minnesota. Pulmonary embolism results from thrombosis, but apparently most often occurs when symptoms of thrombosis are absent. Conner [1] says, "There is reason to believe that the characteristic local signs of thrombophlebitis appear only after the occlusion of the vein has been complete and after more or less periphlebitic inflammation has been added." This may explain why embolism occurs when signs of thrombophlebitis are absent rather than in cases of frank phlebitis. A thrombus completely occluding a vessel would, perhaps, not become detached so easily as would the thrombus floating in the blood stream and attached only over a relatively small area. In postoperative cases resulting in pulmonary embolism clinical evidence of thrombosis is not often observed.

The symptoms of embolism usually appear unexpectedly, following some minor exertion to which the patient has not been accustomed for some days, such as getting out of bed; but embolism occasionally takes place during sleep, when the detachment of the blood clot from its place of origin cannot be blamed on exertion. The symptoms are substernal or precordial pain, dyspnea, cyanosis or pallor, sweating and often anxiety with fear of impending disaster. Mental symptoms, such as coma, may or may not be present. Death may take place suddenly, within a few minutes, or after several hours or days. The suddenness of death probably depends on the size of the embolus, one sufficiently large to occlude the common pulmonary artery usually causing death quickly. In some instances showers of small emboli reach the lungs, ordinarily

* From the Department of Pathology, University of Minnesota.

1. Conner, L. A.: A Pulmonary Attack Simulating Primary Lobar Pneumonia, Caused by Pulmonary Embolism and Infarction from a Latent Venous Thrombosis, Arch. Int. Med. **13**:349-360 (March) 1914.

resulting fatally after a relatively long period, or the patient may recover. In fact, some clinicians believe that most of the cases of postoperative pulmonary complications are embolic in nature. In case of delayed fatal termination, blood may appear in the sputum, especially if infarction has taken place. Such infarcts, if due to a septic embolus, may have the appearances of septic embolic pneumonia.

De Quervain,[2] in reporting 211 cases of postoperative pulmonary embolism, stated that it occurred most frequently at the end of the first and the middle of the second postoperative weeks. In my series of thirty-one postoperative cases it took place seventeen times during the first week, ten times in the second week and in one instance two and one-half months after operation. In this last case symptoms of embolism first appeared on the eighth postoperative day, and again five days before the final embolism.

Postmortem Observations in Pulmonary Embolism.—Cyanosis, which may have been pronounced at the time of death, usually has disappeared by the time the necropsy is performed. Edema of the subcutaneous tissues may or may not be demonstrable. Usually the right ventricle and auricle are found distended. If the heart is removed before the pulmonary artery and its two main branches are examined, the embolus may be overlooked. The embolus may be found obstructing the right or left pulmonary artery, or riding over the bifurcation, filling the pulmonary artery, or even extending back into the right ventricle. The embolus may be made up of many pieces of blood clot, or be a long folded or coiled mass. The external surface of such an embolus usually shows fine corrugations (the lines of Zahn) and has a red, white or mottled appearance. If, instead of a single large embolus, there has been a shower of small emboli, these will be found in the smaller branches of the pulmonary arteries. Infarcts are not infrequently present. Embolism is apparently more frequent in the right lung than in the left. According to de Quervain, embolism of the right lung predominates over that of the left in the relation of 4 to 3. With the smaller emboli the right lower lobe is most frequently involved.

In delayed death the emboli may propagate in the pulmonary arteries and become adherent, so that it is sometimes difficult to distinguish between embolism and primary thrombosis of the pulmonary artery. The lungs may be normal or show edema and congestion. In slow deaths, infarcts, bronchopneumonia or, in the case of infected emboli, abscesses may be present. The liver, spleen and kidneys show acute passive congestion.

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2. De Quervain, F.: Thrombose et embolie post-opératoires, Schweiz. med. Wchnschr. **55**:497-505, 1925.

The source of the embolus or emboli may or may not be found. Many are probably missed, because a sufficiently thorough search cannot be made. In de Quervain's series the primary site was not found in 16 per cent. In 313 cases reported from the Mayo Clinic by Henderson [3] the probable source was determined in 201. In my series the source was found in forty-five, i. e., in 61 per cent of the seventy-three cases.

Examination of 9,275 necropsy records in this department reveals seventy-three cases in which death was due to pulmonary embolism. Of these, seventy were recorded between Jan. 1, 1910 and Jan. 1, 1927, during which time there were 8,273 necropsies, an incidence of 0.84 per cent.

The seventy-three cases fall rather readily into four groups: I *A*, posttraumatic, fifteen cases; I *B*, posttraumatic with operation in consequence of the injury, eight cases; II, postoperative, thirty-one cases; III, postpartum, three cases; IV, medical, sixteen cases.

I. POSTTRAUMATIC EMBOLISM

The finding of fifteen strictly posttraumatic instances of pulmonary embolism and of eight additional cases, in which operation was performed because of the injury sustained, is of considerable interest and importance. This shows that the possibility of thrombosis and embolism after trauma is greater than it is usually thought to be. A brief summary of each of the cases follows.

GROUP A

CASE 1.—A woman, aged 65, fell, fracturing the neck of the left femur. Satisfactory progress was made, and the patient was in good condition at 5 a. m., fourteen days after the accident. At 6 a. m. she was found dead. Necropsy revealed an embolus in both pulmonary arteries, and another at the junction of the superior and the inferior vena cava. Hemorrhage was present in the tissues about the fracture. The source of the embolus was not determined.

CASE 2.—A man, aged 51, with tabes dorsalis, had been struck by an automobile, and sustained cerebral concussion and fracture of the left internal malleolus. The temperature was 103.5 F. four days before death. Two days before death right hemiplegia developed. He died twelve days after the accident. Necropsy revealed an embolus in the right pulmonary artery; hemorrhage into the left basal ganglia of the brain; thrombosis of the right iliac and femoral veins; multiple fractures of the ribs, and syphilitic aortitis.

CASE 3.—A woman, aged 79, fell and fractured the neck of the left femur. One week before death the left leg began to swell. She died seventy-five days after the fall. Necropsy revealed marked edema of the entire left leg; an embolus in the left pulmonary artery; the right pulmonary artery free from emboli; thrombosis of the left femoral vein; no evidence of infection or tearing of the muscles in the region of the fracture of the surgical neck of the femur, and fracture of the right humerus.

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3. Henderson, E. F.: Statistical Study of 313 Proved Cases of Pulmonary Embolism, Proc. Weekly Staff Meeting Mayo Clinic **1**:197 (Dec. 15) 1926.

CASE 4.—A man, aged 38, was struck by an automobile, while he was intoxicated. He had some fever, as high as 101 F. The leukocyte count was 15,000. A roentgenogram did not reveal any fractures. He died six days after the injury occurred. Necropsy revealed: the left hip and thigh swollen; slight abrasions and swelling of the left forearm; a bruise over the left biceps; the left hand swollen; small abrasions of the left thigh; the right pulmonary artery occupied by a large embolus; a few small interstitial hemorrhages in the muscles of the left thigh, and a moderate edema. Thrombosed veins were not found.

CASE 5.—A woman, aged 38, suffered a slight injury of the left knee followed by considerable pain. The leg was in a cast for about two weeks. Edema of the left ankle appeared several days before death. Three quarters of an hour before death she was seized with intrathoracic pain and dyspnea. Death occurred seventeen days after the injury. Necropsy revealed edema of the left ankle and the lower half of the left leg; an embolus in the pulmonary artery and both the right and the left branches; an infarct in the left lower lobe, and thrombosus of the left popliteal vein, extending into the short saphenous vein, several other small tributaries and the femoral vein. The cavity of the left knee joint contained about 5 cc. of slightly blood-stained fluid. The synovial ligaments were slightly congested.

CASE 6.—In a woman, aged 65, with no history, necropsy revealed: an embolus occupying both pulmonary arteries, and double fracture of the left femur, with hemorrhages about them. Thrombosed veins were not found.

CASE 7.—A man, aged 59, was struck by an automobile, sixteen days before his sudden death, sustaining fracture of the upper third of the right fibula. About one week later he had fever, with a temperature as high as 102 F., for three days. The leukocyte count was 15,000. The fever and leukocytosis were unaccounted for. The course was otherwise favorable and he had been up and around for three days. There was cyanosis and air hunger for ten minutes before death. Necropsy revealed: discoloration of the skin over the upper half of the right lower leg; a folded up embolus 23 cm. long in the common pulmonary artery, and an infarct in the upper lobe of the right lung. An antemortem blood clot 12 cm. long was forced from the right femoral vein. Dissection of the lower part of the right leg revealed thrombosis of the posterior tibial and peroneal veins, extensive hemorrhage and edema of the muscles of the right leg.

CASE 8.—A woman, aged 48, fell, fracturing the right femur. She experienced a sudden sinking spell with a blood pressure reading of 72 systolic and 48 diastolic, twelve days after the fall. Five days before death the leukocyte count was 35,000; three days before death, 33,000. The temperature at times was as high as 102 F. She died twenty-five days after the injury occurred. The postmortem observations were: embolism and thrombosis of the pulmonary arteries; an infarct in the right lower lobe; thrombosis of the lower end of the vena cava and the right common iliac vein.

CASE 9.—A man, aged 65, fractured the first lumbar vertebra in an automobile accident; he ran a low grade temperature for one week. The day before death he was wakened from sleep with a sudden sharp pain in the lower sternum and shortness of breath. Nine hours later he suddenly became comatose and had weakness of the right side of the body. Later pulmonary edema and fever appeared. Death occurred twenty-eight days after the accident. Necropsy revealed: cardiac hypertrophy (575 Gm.); bilateral bronchopneumonia; multiple emboli in the right pulmonary artery; thrombosis of the right common iliac vein, and the brain normal.

CASE 10.—A man, aged 78, sustained a fracture of the right femur. He made good progress and was up and around on the day of his death, which occurred ninety days after the injury. Necropsy revealed: a large twisted and folded embolus in the right pulmonary artery; thrombosed branches of pulmonary arteries; bilateral lobar pneumonia, and thrombosis of the prostatic veins.

CASE 11.—A man, aged 50, fell down an elevator shaft, fracturing the pelvis. He died four days later. Necropsy revealed: a large folded embolus in the left pulmonary artery; thrombosed pulmonary vessels on section; rupture of the bladder with infiltration of urine and blood into the soft tissues, and fracture through the symphysis pubis and the left ramus of the pubis. The source of the embolus was not determined.

CASE 12.—A man, aged 52, was caught between the elevator and the floor, and received crushing injuries about the hips. The left ramus of the pubis was fractured. He was making good progress, but died suddenly twenty-one days after the injury. Necropsy revealed: multiple contusions about the hips, with ulceration and purulent exudate; an embolus 16 cm. in length in the common pulmonary artery; considerable hemorrhage in the pelvic connective tissue; fracture of the left ramus of the pubis, and thrombosus of the right common, external and internal iliac veins.

CASE 13.—A woman, aged 30, was injured in an automobile accident, sustaining a compound fracture of the left middle finger, a fracture of the left index finger, and injury to the left hip. The course was favorable until her sudden death five days after the accident. Necropsy revealed: slight edema of the ankles; two emboli in the pulmonary artery, one 7 cm., the other 12 cm. in length, and several small emboli in the parenchymal branches; fracture of the left ilium near the sacro-iliac synchondrosis, and slight regional intramuscular hemorrhage. Thrombosed veins were not found.

CASE 14.—A man, aged 42, received a gunshot wound of the groin and died eight days later. The temperature was septic. There was gas bacillus infection. Necropsy revealed: an embolus in the branch of the left pulmonary artery, and an infarct in the lower lobe of the right lung. Thrombosed veins were not found.

CASE 15.—A man, aged 36, fractured the surgical neck of the right femur. The course had been uneventful and the patient was about to be discharged, when a sudden sharp pain appeared in the right groin. Almost immediately there was severe dyspnea and cyanosis. He became unconscious and died in three or four minutes, six weeks after injury. Necropsy revealed: laceration of the muscles and a large amount of hemorrhage about the fracture; embolus of both the right and the left pulmonary arteries, extending back into the right ventricle, and infarcts in both lower lobes. The source of the embolus apparently was not searched for.

These fifteen cases are summarized in table 1. In this group there are several interesting points. With the exception of cases 4, 5 and 14, there was in each case a fracture which required rest in bed because of its location. In none of the cases, unless case 13, in which there was a compound fracture of the finger in addition to the fracture of the ilium, was there a compound fracture. Another striking thing is the time at which embolism took place. In only six of the fifteen cases, did it occur within the first two weeks. In case 10 the embolism did not take

place until the ninetieth day. Postoperative embolism, on the other hand, is most common during the first two weeks, and rare after a month. Strauss [4] also calls attention to the late appearance of embolism in traumatic cases.

In five of the eight cases in which the thrombus was found it was located at or near the site of the injury, so that it may be attributed to direct trauma to the veins. In cases 2, 9 and 10 the site of the thrombus does not correspond closely to that of the injury, but it is difficult to be sure that these thrombosed veins were not injured in the respective accidents. One may, perhaps, rightly object to the inclusion of case 14 in the group, and say that death was due, not to embolism, but to gas bacillus infection, and that the embolus arose in an infected field. Case 4 is of importance because minor superficial

TABLE 1.—*Posttraumatic Pulmonary Embolism*

Necropsy	Sex	Age	Pathologic Diagnosis	Days after Accident	Source of Embolus
1	F	65	Fractured left femur....	14	Undetermined
2	M	51	Fractured tibia.....	12	Femoral and iliac
3	F	79	Fractured femur.....	75	Left femoral vein
4	M	38	Minor injuries.....	6-7	Undetermined
5	F	38	Knee injury.....	17	Left popliteal
6	F	65	Fractured femur.....	..	Undetermined
7	M	59	Fractured fibula.....	16	Posterior tibial
8	F	48	Fractured right femur..	25	Vena cava and right common iliac
9	M	65	Fractured vertebra.....	28	Right common iliac
10	M	78	Fractured right femur...	90	Pelvic veins
11	M	50	Fractured pelvis.....	4	Undetermined
12	M	52	Fractured pelvis.....	21	Right common iliac
13	F	30	Fractured pelvis.....	5	Undetermined
14	M	42	Gunshot wound groin...	8	Undetermined
15	M	36	Fractured femur.....	42	Undetermined

abrasions and bruises and small hemorrhages into the muscles of one thigh were the only demonstrable injuries. Several of the patients had unexplained rises of temperature and leukocytosis after their injury. A number of them were thought to be making satisfactory progress until the embolism took place. It should also be noted that eleven of these patients were more than 40 years of age and nine of them 50 or more.

The eight cases in which operation was performed because of the injury are as follows.

GROUP B

CASE 1.—A man, aged 45, fractured the left patella about three and one half months before death. Eight weeks before death the patella was sutured without drainage. For the next twenty-five days he had a daily rise of temperature, varying from 99 to 101 F. Thereafter it was normal. The leg was swollen above and below the knee from the time of operation. He died fifteen minutes after the onset of symptoms of embolism which were faintness, dyspnea, cyanosis and

4. Strauss, M.: Lungenembolie als Spätunfallsfolge, Beitr. z. klin. Chir. **88**:637-640, 1914.

unconsciousness. Necropsy revealed: an operative wound completely healed and free from evidences of infection; the entire left leg swollen and with edema below the middle point of the thigh; an embolus occluding both pulmonary arteries, and thrombosis of the left femoral vein and its branches from Hunter's canal down to the popliteal vein.

CASE 2.—A man, aged 50, fell from a ladder, fracturing the wrist and the right patella. The patella was sutured two days later. His condition was good until sudden death twelve days after the injury. Necropsy revealed: an operative wound, unhealed; a considerable amount of bloody fluid in the joint cavity; discoloration of the skin below the knee joint; a bruise and discoloration on the left forearm; laceration of the lip, an embolus in the common pulmonary artery and its branches; the right popliteal vein thrombosed together with several of its deep muscular branches, and considerable subcutaneous and intermuscular hemorrhage in the right calf.

CASE 3.—A man, aged 30, was struck on the head with a bottle two weeks before his death and the scalp was bruised but not cut. Right hemiplegia resulted. A decompression operation was performed nine days before his sudden death. Necropsy revealed: swelling and softening of the tissue about the operative wound; vegetative endarteritis of the root of the aorta; emboli in both pulmonary arteries; abscess of the right lobe of the cerebellum; thrombosis of dural sinuses, and no cranial fracture.

CASE 4.—A man, aged 25, received a gunshot wound of the abdomen with perforations of the intestine. The perforations were sutured and the course was favorable until sudden death two days after the injury and operation. Necropsy revealed: bloody fluid and fibrinous adhesions in the peritoneal cavity and pus between the coils of the intestine; four perforations sutured; a bullet buried in the floor of the iliac fossa; extensive hemorrhage in the same region; a large embolus in the left pulmonary artery; a small embolus in the right pulmonary artery, and thrombosis of the right external iliac vein(?).

CASE 5.—A woman, aged 55, slipped and fell, injuring the right knee. There was a minor abrasion over the right patella. Pain was present in the right leg when the patient walked and she was put at rest for ten days. Then the prepatellar bursa was excised. After operation the patient complained of severe pain in the calf of the leg. The temperature at times rose to 100 F. Suddenly the patient became dyspneic and cyanotic and died in ten minutes, on the forty-eighth day after the accident and the eighteenth postoperative day. Necropsy revealed: no evidence of infection in the operative wound; two emboli 2.5 by 1 cm. in the pulmonary artery; the right popliteal vein thrombosed, and no hemorrhage in the calf of the leg.

CASE 6.—A man, aged 65, fractured the left femur eleven days before death. Open reduction with plating was performed four days before death. The temperature was 100.6 F. on the first day after the operation. Death was sudden. Necropsy revealed: pus just beneath the operative incision in the skin; no pus in the depths of the wound; a large curled up embolus in the common pulmonary artery; a thrombus in the lower end of the vena cava, and small antemortem clots which were expressed from the veins of the left leg.

CASE 7.—A man, aged 63, was struck in the abdomen by a heavy board three weeks before death. Laparotomy was performed a few hours after the accident and a ruptured coil of the ileum was sutured. The postoperative course was good until four days before death when difficulty in breathing began and con-

tinued until death, gradually becoming more severe. He had a little fever from the time of the accident. On account of urinary retention the catheter was introduced. Death occurred three weeks after the accident and operation. Necropsy revealed: a wound infection; purulent pericardial fluid; the right and left pulmonary arteries filled with emboli; an infarct in the lower lobe of the left lung; thrombosis of the veins of the prostatic plexus, and purulent cystitis.

Case 8.—A man, aged 49, fell from a scaffold and sustained a left inguinal hernia thirteen days before death. Herniotomy was performed eight days later. He died suddenly on the fifth postoperative day. Necropsy revealed: a sticky exudate, but no pus in herniotomy wound; an embolous 5 by 1 cm. in the common pulmonary artery, and thrombosis of the left common and external iliac veins. The lower end of the thrombus in the external iliac vein was immediately underneath the operative wound.

Table 2.—*Combined Postaccident and Postoperative Pulmonary Embolism*

Necropsy (Sex and Age)	Clinical Diagnosis	Operation	Untoward Symptoms	Number Days: Postaccident	Number Days: Postoperative	Necropsy Diagnosis	Wound Infected	Source of Embolus
1 (M 45)	Fractured patella	Suture patella	Temperature 29th day 99-101 F.	105	56	.....	No	Left femoral
2 (M 50)	Colles fracture; fractured patella	Suture patella	0	12	10	Subcutaneous and muscle hemorrhage	?	Right popliteal
3 (M 30)	Left hemiplegia	Decompression	0	14	9	Cerebellar abscess	?	Cerebral sinus
4 (M 25)	Gunshot wound of abdomen	Suture perforated bowel	.....	2	2	Local peritonitis	..	External iliac (?)
5 (F 55)	Minor abrasions	Excision patellar bursa	Pain in leg	48	18	Hemorrhage right calf	No	Right popliteal
6 (M 65)	Fractured left femur	Open reduction with plating	Temperature 2d day 100.6 F.	11	4	.....	Yes	Vena cava; left leg
7 (M 68)	Rupture of bowel	Suture bowel	Temperature	21	21	Purulent bronchitis; cystitis	Yes	Wound and prostatic plexus
8 (M 49)	Left inguinal hernia traumatic (?)	Herniotomy	.....	13	5	.....	?	Left common iliac

These eight cases are summarized in table 2. With the exception of case 5, major operations were performed in each instance, so that it is uncertain whether these cases belong in the posttraumatic or postoperative group. In this group six of the patients were over 40 years of age. In two of the eight cases there was definite, and in three others (2, 3 and 8) questionable, wound infection. The thrombus in each case was formed at the site of the injury, which was also the site of the operation. Embolism occurred earlier in this group than in the strictly accidental cases. Case 3 was rather complicated in that the cerebellar abscess may have been embolic in origin from the vegetative aortitis, and the sinus thrombosis an extension from the abscess. In case 5 the

thrombosis of the popliteal vein had nothing to do with the excision of the prepatellar bursa. Pain in the leg began immediately after the injury and was present before the operation, which was not performed until four weeks after the injury.

II. POSTOPERATIVE EMBOLISM

The details of each case in group II will not be given. Table 3 shows a summary of them, giving the sex, age, type of operation, the number of days after operation when embolism occurred, whether there was

TABLE 3.—*Postoperative Pulmonary Embolism*

Necropsy	Sex	Age	Operation	Days Postoperative	Wound Infection	Source of Embolus
1	M	56	Perforated duodenal ulcer	4	Yes	Undetermined
2	M	64	Gastrectomy	7	Yes	Left iliac
3	F	19	Ventrosuspension; appendectomy	12	No	Common iliacs
4	F	20	Appendectomy	4-5	Stump	Undetermined
5	M	..	Hemorrhoidectomy	7	..	Left internal iliac
6	M	42	Cholecystectomy	12 hrs.	..	Undetermined
7	F	33	Exploratory for abdominal tumor	8	..	Undetermined
8	F	41	Hysterectomy	14	No	Probably pelvic
9	F	45	Cholecystectomy; appendectomy	7	Stump	Left internal iliac
10	F	64	Herniotomy, umbilical	6	No	Varicose veins (?)
11	F	51	Cholecystectomy	10	Yes; peritonitis	Partial necropsy
12	M	59	Varicose veins	10	..	Right saphenous
13	M	66	Cholecystectomy; appendectomy	6	Yes; stump	Undetermined
14	F	63	Varicose veins (otitis media)	75	..	Undetermined
15	F	58	Hysterectomy	8	No	Left iliac
16	F	55	Herniotomy, umbilical	5	Yes	Varicose veins (?)
17	F	30	Ectopic pregnancy	12	No	Left internal iliac
18	M	47	Appendectomy	9	Yes	Undetermined
19	F	60	Colostomy for anal granuloma	1	..	Undetermined
20	M	83	Prostatectomy	6	Gangrenous cystitis	Undetermined
21	M	64	Cystotomy	..	Yes	Right femoral and iliac
22	M	65	Herniotomy, right inguinal	18	Yes	Operative field
23	M	40	Herniotomy, bilateral inguinal	7	No	Left leg
24	F	24	Appendectomy	4	Yes	Right internal iliac
25	F	23	Appendectomy	Few	Stump	Right iliac
26	F	30	Hysterectomy; oophorectomy	7	Yes	Left ovarian
27	F	49	Perineorrhaphy	14	No	Undetermined
28	M	58	Laparotomy; intestinal obstruction	9	Yes; peritonitis	Undetermined
29	F	20	Appendectomy	6	Yes; stump	Undetermined
30	F	67	Amputation, right (gangrene)	1	..	Right femoral
31	M	41	Appendectomy	6	Yes	Right iliac

wound infection and the source of the embolus. There were thirteen men and eighteen women patients. In twenty-one instances the patients were forty-one or more years of age; the youngest was 19. Without exception the operative procedure was below the level of the diaphragm. There were four on the upper part of the abdomen; fourteen on the lower part of the abdomen; four on both the upper and the lower part of the abdomen; one hemorrhoidectomy; one perineorrhaphy; four herniotomies, and three on the lower extremities. As mentioned previously, embolism took place seventeen times in the first week, ten times in the second week and once after two and one-half months. Infection of the operative area was present in seventeen, denied in six and

not mentioned in eight cases. The location of the primary thrombosis was determined in sixteen of the patients. Varicose veins were suspected in cases 10 and 16 in each of which there had been an umbilical herniotomy. In the remaining fourteen cases in which the source of the embolus was determined, it was in a place where it could be due to direct trauma to a vessel during operation, or to an extension from the operation field. Perhaps case 30 should not be included as a postoperative embolism in the strictest sense, since the amputation was done

TABLE 4.—*Postpartum Pulmonary Embolism*

Necropsy	Sex	Age	Delivery	Puerperium	Temperature	Days Postpartum	Necropsy Diagnosis	Source of Embolus
1	F	33	Normal	Normal	Normal	12	Subacute infectious endometritis	Vaginal and uterine wall veins
2	F	36	Normal	.....	99-100 F.; 101 F. on tenth day	11	.....	Undetermined
3	F	30	Normal	Normal	99 F. day of death	6	Subinvolution; low grade infection	Parametrial veins

TABLE 5.—*Medical Pulmonary Embolism*

Necropsy	Sex	Age	Pathologic Diagnosis	Source of Embolus
1	M	67	Hypertension; cardiac failure.....	Right auricle
2	M	50	Carcinoma of lung.....	Pelvic veins
3	M	50	Nephroma	Left femoral
4	F	73	Hypertension; cardiac failure.....	Right auricle
5	M	40	Otitis media; mastoiditis.....	Left leg
6	F	65	Bronchopneumonia	Left iliac
7	F	68	Varicose veins	Varicose veins
8	M	41	General paralysis	Undetermined
9	M	80	Prostatic obstruction	Undetermined
10	M	43	Hypertension; cardiac failure.....	Right auricle
11	M	58	Hypertension; cardiac failure.....	Right auricle
12	M	71	Hypertension; cardiac failure.....	Left common iliac
13	F	74	Hypertension; cardiac failure.....	Right auricle; vena cava
14	M	30	Pulmonary tuberculosis	Left common iliac
15	F	38	Encephalomalacia; otitis media.....	Cerebral sinus
16	M	43	Cerebrospinal syphilis	Undetermined

for gangrene, and at autopsy both femoral artery and vein were found thrombosed, although the pathologist's opinion was that the venous thrombosis was not as old as the arterial.

III. POSTPARTUM EMBOLISM

The three cases of postpartum embolism are summarized in table 4. This, of course, is too small a number to give much information. All three patients were in the fourth decade, before the age when embolism is most common. In the two in whom the source of the embolus was determined, it was in connection with the uterus, and in each case there was inflammation of the uterus.

IV. MEDICAL EMBOLISM

The sixteen medical cases recorded in table 5 show in what a wide variety of conditions embolism may occur. With but two exceptions the patients were more than 40 years of age, and ten of them 50 or more. In the six heart cases, all of which were essential hypertension with cardiac failure, the thrombus was located in the right auricle in four, in the left common iliac vein in one and in either the right auricle or the vena cava in one. It is interesting that in cases 3, 5, 6, 12 and 14 the thrombi arose in the left iliac vein or in its tributaries. Two cases of otitis media (5 and 15) are striking in that in the former the thrombus developed in the leg and in the latter in the cerebral sinuses.

Numerous statistics are available as to the postoperative incidence of fatal pulmonary embolism. Wilson [5] reported forty-seven instances in 63,573 operations. Lockhart-Mummery's [6] figures are as follows: nine in 5,406 operations; six in 7,327 operations; twelve in 11,804 operations; eight in 17,757 operations. Naegeli [7] reported twenty-one in 15,343 operations or 0.14 per cent and forty-three in 4,916 autopsies or 0.87 per cent. Lockhart-Mummery reported from Adelaide Hospital 2.5 per cent of postoperative deaths as due to pulmonary embolism, and from St. Mark's 5 per cent of deaths. Snell [8] says, "Pulmonary embolism is responsible for from 8 to 10 per cent of all postoperative deaths at the (Mayo) Clinic, the incidence by cases being about 0.2 per cent."

The incidence of postoperative pulmonary embolism is better understood when it is considered according to the sites of operation. Here Wilson's statistics on 63,573 operative cases and de Quervain's on 76,799 are of value. Wilson's figures are given in table 6.

De Quervain's figures are given in table 7.

Wilson's statistics show a much lower incidence of postoperative pulmonary embolism than de Quervain's.

These statistics show that embolism is most common after operations on the prostate, and that it is next in frequency after operations on the intestinal and biliary tracts. The incidence of embolism after thyroid operation is low in the two series. Its occurrence after appendectomy and herniotomy is strikingly low in each series. There

5. Wilson, L. B.: Fatal Postoperative Embolism, Ann. Surg. **56**:809-817, 1912.

6. Lockhart-Mummery: Discussion on Postoperative Pulmonary Embolism, Brit. M. J. **2**:850-854, 1924.

7. Naegeli, T.: Thrombose und Emboli, Schweiz. med. Wchnschr. **55**:520, 1925.

8. Snell, A. M.: Obesity in Relation to Postoperative Embolism, Proc. Weekly Staff Meeting Mayo Clinic **1**:198-199 (Dec. 15) 1926.

is a marked difference in the incidence after appendectomy as compared with operations on other portions of the intestine. A satisfactory explanation of this difference has not been offered.

Another factor of importance would seem to be the extent of the operation. Appendectomy is usually less extensive than other intestinal operations. Henderson, for reasons to be given a little later, says, "The site of operation seems to have little to do with the cause of pulmonary embolism."

TABLE 6.—*Statistics from 63,573 Cases of Postoperative Pulmonary Embolism (Wilson)*

Type of Operation	No. of Operations	Emboli	Per Cent
Blood vessels	1,372	2	0.14
Thyroid	3,266	2	0.06
Mouth	2,281	1	0.05
Stomach and duodenum	2,391	3	0.12
Gallbladder	4,597	9	0.19
Small intestine	889	1	0.26
Appendix	9,906	4	0.04
Colon and rectum	2,530	5	0.20
Hernia	4,501	5	0.11
Kidney	900	1	0.11
Prostate	601	4	0.66
Uterus, tubes, ovaries	7,993	10	0.13
Breast	1,346	0	0

"No fatal embolism in 449 vaginal hysterectomies, though there was one in every 342 abdominal hysterectomies."

TABLE 7.—*Statistics from 76,799 Cases of Postoperative Pulmonary Embolism (De Quervain)*

Type of Operation	No. of Operations	Emboli	Per Cent
Prostate	356	7	1.99
Gastro-intestinal	5,070	54	1.06
Thorax	1,333	5	0.37
Bile passages	946	8	0.84
Kidneys	508	2	0.39
Extremities	7,996	16	0.20
Gynecologic	2,341	5	0.21
Appendix	10,089	10	0.10
Hernia	11,475	17	0.15
Thyroid	5,879	2	0.034

The site of the primary thrombosis in embolism following operation may be within the operative field or distantly removed from it. The three common sources are the femoral, iliac and pelvic veins, and it is more common on the left side than on the right. De Quervain found the distribution given in table 8.

Trinkler [9] found thromboses of the veins of the lower extremities in twenty-seven cases of appendicitis. The thrombi were always on the left side. In my postoperative group the primary thrombosis was in the

9. Trinkler, N.: Beiträge zur Entstehung der Thromben in den Venen der unteren Extremität vorzugsweise der linken, Arch. f. klin. Chir. **120**:653 and 657, 1922.

iliac, femoral or pelvic vein in fourteen instances, six on the left side, seven on the right side and one bilateral. According to de Quervain, Fehling [10] found the primary thrombosis twice as common on the left side as on the right.

Henderson found that the embolus was in the iliac vein, femoral vein, pelvic veins or prostatic plexus in 83 per cent of his 201 cases in which its probable source was determined. He states, further, concerning the cases in which the iliac and femoral veins were the sources that, "In 27 per cent of this group of 106 cases the operation had been extra-abdominal. The number of upper and lower abdominal operations was about the same; this led to the belief that the site of operation may not have as much to do with causing embolism as was formerly supposed."

The occurrence of thrombosis and pulmonary embolism following operations, childbirth and various medical conditions has long been recognized, but its development as a result of trauma is apparently not so well known. Eisendrath [11] says, "Not infrequently thrombosis of

TABLE 8.—*Distribution of Sources of Primary Thrombosis (De Quervain)*

Vein	Right	Left	Bilateral	Side Not Indicated
Hypogastric	5	9	2	43
External iliac	12	14	2	4
Femoral	53	60	16	17
Saphenous	1	5	0	2

the deep veins of the lower extremity occurs in fractures of the tibia and fibula or of the patella or femur. A marked swelling of the entire limb occurs, which is far greater than that ordinarily accompanying such a fracture. . . . In a few cases an embolus has been detached and has produced pulmonary embolism." According to Aufrecht,[12] venous thrombosis as a result of trauma is not rare. Bruns,[13] in 1886, was able to collect thirty-four cases of embolism following fractures and added one of his own. Of these thirty-five cases, thirty were fatal and necropsies were performed in twenty-three. In three instances the embolus stopped in the right side of the heart. Of these thirty-five cases, twenty-four were fractures of the leg, seven of the femur, one of the patella and three of the upper arm. Only two were compound fractures.

10. Fehling, cited by de Quervain (footnote 2, p. 501).

11. Eisendrath, D. N.: Keen's Surgery, Philadelphia, W. B. Saunders Company, 1914, vol. 2, p. 99.

12. Aufrecht, E.: Nothnagel's Encyclopedia of Practical Medicine (American Edition): Diseases of the Bronchi, Lungs and Pleura, Philadelphia, W. B. Saunders Company, 1903, p. 740.

13. Bruns, P.: Weitere Beiträge zur Fracturenlehre, Beitr. z. klin. Chir. **2**:1-18, 1886.

In this series the embolism took place between the thirteenth and twentieth days in eleven cases. In the group, in which the age was given, only five patients were under 40 years of age. The age was not stated in six instances. He also mentions three cases, collected by Güterbock,[14] of embolism following contusions. Lotheissen,[15] in 1902, added one clinical case, reported by Puterman,[16] following fracture of the leg. He also collected five fatal cases following contusions and four fatal cases after tearing of tendons and muscles. Of these nine cases, eight were injuries of the lower extremities. Daus[17] (1913) collected thirty-four cases from the literature and added one of his own in which thrombosis followed an injury. In the available literature, I have found thirty-six additional cases of posttraumatic thrombosis and pulmonary embolism.

Altogether 119 cases have been recorded, but they are seldom described in sufficient detail to justify a tabular summary. A summary of my twenty-three cases has already been given. From the total 142 cases certain general conclusions may be drawn:

1. Posttraumatic thrombosis and embolism are not at all rare.
2. A simple fracture was present in a majority of instances, but only rarely a compound fracture.
3. In a number of instances there was only minor bruising of the soft tissues without fracture of a bone.
4. The thrombus always developed at the site of the injury.
5. The interval between trauma and pulmonary embolism is longer than that between operation and embolism.
6. The age distribution appears to be about the same as that of other forms of pulmonary embolism.
7. Injuries resulting in embolism usually involve the lower extremities.

The question of the etiology of embolism is closely bound up with that of thrombosis. The factors which are generally considered important in the etiology of thrombosis are (1) slowing of the blood stream; (2) injury of the endothelium; (3) changes in the composition of the blood. There is no general agreement as to the relative importance of these three factors.

1. *Slowing of the Blood Stream.*—This is considered an important cause of thrombosis by practically all writers. The majority believe that stasis alone without endothelial injury never results in thrombosis;

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14. Güterbock, cited by Bruns (footnote 13).

15. Lotheissen, G.: Zur Embolie der Lungenarterie nach Verletzungen und operativen Eingriffen, Beitr. z. klin. Chir. **32**:655-686, 1902.

16. Puterman, cited by Lotheissen (footnote 15, p. 660).

17. Daus, S.: Ueber traumatische Thrombose, Deutsches Arch. f. klin. Med. **112**:348-368, 1913.

but a few believe that stasis associated with changes in the blood is sufficient. In favor of the importance of slowing of the blood stream is the great preponderance of venous over arterial thrombi, the frequency of thrombosis of the auricular appendages in cardiac failure and the infrequency of thrombi on atheromatous ulcers of the aorta.

Many surgeons attribute the greater frequency of postoperative thrombosis and embolism after abdominal operations to the slowing of the venous circulation in the lower half of the body which results from the absence of muscular contractions in the abdomen and lower extremities. Some have acted on this theory by the use of "bed gymnastics" and by attempting to shorten the period of rest in bed after operation.

2. *Injury of the Endothelium.*—The majority of writers believe that endothelial injury is necessary for thrombosis. The endothelial lining of the vessel may be damaged by (1) trauma, (2) extension of infection from a localized area into the adjacent veins (for example, lateral sinus thrombosis from otitis media) and (3) bacteria or their toxins in the circulating blood (for example, thromboses following pneumonia or typhoid fever). Trauma and direct extension of infection into a vessel are obvious causes of certain thrombi. That bacteria or their toxins in the blood may cause endothelial damage and thrombosis is inferred from the frequent association of thrombosis with infectious diseases and infections.

The rôle of infection in thrombosis: Some workers go so far as to say that there cannot be any thrombosis in the absence of infection. "Kretz [18] reported that in 6,500 autopsies he had seen no thrombosis without previous infection." Helly [19] found 240 thromboses in 2,225 necropsies and in only six was he unable to establish infectious foci. According to de Quervain 67 per cent of emboli arise in septic fields. Henderson found postoperative infections in 60 per cent of his 267 cases of postoperative embolism. In my series of thirty-one postoperative cases, wound infection was present in seventeen and denied in six. Apparently infection of the wound is an important contributory factor in pulmonary embolism, but there are cases in which infection cannot be established.

3. *Changes in the Composition of the Blood.*—It is known that thrombi may be produced by intravenous injections of organ extracts, foreign serums and toxic substances, such as snake venom. According to Heusser,[20] a decrease in the sedimentation time of the erythrocytes

18. Kretz, cited by Meyer-Rüegg: Schweiz. med. Wchnschr. **55**:508, 1925.

19. Helly, K.: Thrombose und Embolie, Schweiz. med. Wchnschr. **55**:492, 1925.

20. Heusser, H.: Postoperative Blutveranderungen und Thrombose, Schweiz. med. Wchnschr. **55**:518-520, 1925.

takes place after operations, injuries and infections. Allen [21] finds that after operation "There are definite changes in the erythrocyte count, the leukocyte count, fatty acid content (in obese individuals), the coagulation time (Mill's method), blood calcium content, fibrinogen content, and prothrombin time." It is possible, therefore, that changes in the composition of the blood may be a factor in human thrombosis.

Sex apparenly has no rôle in pulmonary embolism. Henderson's group contained 151 males and 162 females. In my series there were forty males and thirty-three females. Age is usually thought to be of great importance. In de Quervain's series embolism was most common between the ages of 60 and 69 years, and 90 per cent of his patients were over 40 years of age. The average in Henderson's group was 53 years, which, he says, is greater than the average age of the clinic's patients. Wilson, in a series of forty-seven cases, found a fairly even distribution from the fourth to the seventh decade inclusive.

TABLE 9.—*Distribution of Cases by Decades*

Decades	Necropsies	Cases of Pulmonary Embolism	Percentage
11-20	343	3	0.87
21-30	705	8	1.13
31-40	917	9	0.98
41-50	960	17	1.77
51-60	1,113	11	0.90
61-70	814	14	1.71
71-80	306	6	1.96
81 +	54	1	1.85
	5,212	69	Average 1.39

Table 9 shows the distribution of my cases by decades, and also the number of necropsies in each decade. It will be seen that although 71 per cent of the patients were over 40 years of age, the percentage incidence in the different decades is not strikingly different. More necropsies are performed on persons over 40 years old. This suggests that age is not as important a factor as is commonly supposed.

SUMMARY

Seventy-three cases of pulmonary embolism were found in the 9,275 necropsy records in the Department of Pathology of the University of Minnesota. They were divided into four groups: I *A*, posttraumatic, fifteen cases; I *B*, posttraumatic with operation in consequence of injury, eight cases; II, postoperative, thirty-one cases; III, postpartum, three cases; IV, medical, sixteen cases. The patients included forty males and thirty-three females. The age varied from 19 to 83 years. When considered in relation to the number of necropsies

21. Allen, E. V.: Changes in the Blood Following Operation, Proc. Weekly Staff Meeting Mayo Clinic **1**:197 (Dec. 15) 1926.

done in each decade, this series shows practically the same incidence of embolism in all decades after the first. Age is probably not as important a factor as it is usually thought to be.

In the postoperative group, wound infection was present in seventeen cases. In twenty-seven of the thirty-one postoperative cases embolism occurred during the first two weeks.

Apparently the occurrence of thrombosis and pulmonary embolism after injury is not generally well known. One hundred and nineteen cases of posttraumatic thrombosis and embolism were collected from the literature. These together with the twenty-three reported here make a total of 142. From these 142 cases certain general conclusions were drawn. 1. Posttraumatic thrombosis and embolism are not at all rare. 2. A simple fracture was present in a majority of instances, but only rarely a compound fracture. 3. In a number of instances there was only minor bruising of the soft tissues without fracture of a bone. 4. The thrombus always developed at the site of the injury. 5. The interval between trauma and pulmonary embolism is longer than that between operation and embolism. 6. The age distribution seems to be about the same as that of other forms of pulmonary embolism. 7. Injuries resulting in embolism usually involve the lower extremities.

In postoperative thrombosis and embolism the primary site of the thrombosis may lie within the operative field or be distantly removed from it. The iliac, femoral and pelvic veins are the most common sites of the primary thrombosis. The veins of the left side are most often involved. Postoperative pulmonary embolism usually follows operations below the level of the diaphragm, and only rarely those above the diaphragm, and is most common following operations on the prostate, intestinal and biliary tracts.

Thrombosis and embolism develop in a great variety of medical conditions, and the thromboses are usually situated in the veins of the lower extremities, as in postoperative cases, often independent of the major anatomic lesions.

COLOR OF THE SKIN AND CORIUM PIGMENTATION

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During the autumn of 1919, an exceedingly interesting case of hyperpigmentation came to my attention. This case has been discussed by Ormsby and Mitchell [1] (1920), also by Warthin, Crane and Jackson [2] (1924). A preliminary statement concerning my observations has been made (Strong,[3] 1922). A peculiar feature of the case was a bluish to slate gray aspect of the skin color on the face and elsewhere, which immediately suggested to me a pigmentation deeper in the skin than normal.

On examination of histologic material, subsequently obtained through the kindness of Dr. Ormsby, an abnormal occurrence of melanophores was found in the superficial corium. The epidermis was practically devoid of pigment. Since then, I have made a careful search of dermatologic literature for similar cases and at the same time have studied the color problems involved.

The causes of skin color have been well discussed by Audry [4] (1896), Mandoul [5] (1903), Evans [6] (1907) and Jordan [7] (1911). Jordan [8]

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1. Ormsby, O. S., and Mitchell: Hyperpigmentation, Arch. Dermat. & Syph. **1**:474-476, 1920.

2. Warthin, A. S.; Crane, A. W., and Jackson, J. B.: Pigmentation of the Skin (Addison's Disease) Associated with Lymphosarcoma Involving Particularly the Retroperitoneal Lymph Nodes of the Solar Plexus Region, Arch. Dermat. & Syph. **10**:139-162 (Aug.) 1924.

3. Strong, R. M.: Hyperpigmentation and So-Called Blue Skin, Anat. Record **23**:40, 1922.

4. Audry, C.: Quelques notions sur la forme et le couleur de la Peau et de ses annexes, Clin. de la Fac. de méd. de Toulouse **2**:43-53, 1896; J. d. mal. cutan. et syph. **13**:853-865, 1901.

5. Mandoul, H.: Recherches zur les Colorations tegumentaires, Ann. d. sc. nat. zool. et paléontol. **18**:225-463, 1903.

6. Evans, W. H.: Erasmus Wilson Lecture on Leucoderma and Analogous Changes in the Pigmentation of the Skin, Lancet **1**:407-410, 1907.

7. Jordan, H. E.: A Comparative Microscopic Study of the Melanin Content of Pigmented Skins with Special Reference to the Question of Color Inheritance among Mulattos, Am. Naturalist **45**:449-470, 1911.

8. Jordan (footnote 7, p. 465).—"The degree of skin coloration is due to the variable number of pigment granules in the cells of the rete mucosum Malpighi involving incidentally a variable number of more superficial cells. (2) The pigment granules (melanic) of all skin (albinos excepted) are identical in size (practically), shape and color (without qualification). (3) The ascending scale of morphological conditions paralleling a progressively deepening grade of pig-

recognized the importance of the number of melanin pigment granules per cell and the number of pigmented epidermal cells in skin coloration. He observed that the black color of a full-blooded negro is due to the density of the melanin pigment granule distribution in the epidermis.

In normal skin color, there is a well known yellow component which gives a more or less apparent brownish tint. This, of course, may be slight or, on the other hand, may be conspicuous, as in the brown races or in skin much exposed to the weather. This yellow component has been measured in the negro by Jordan (1911), Davenport [9] (1913) and Todd and Van Gorder [10] (1921).

According to Vörner [11] (1905), there is a yellow, fat-soluble pigment in human skin, which he observed in frozen sections. I have not encountered such a pigment, however, even when fat solvents were avoided; nor have I heard of any confirmation of Vörner's observations.

A much more important cause for the yellow component, in my judgment, may be found in the melanin granules of the epidermis. When viewed under the microscope with high magnifications, melanin granules are yellow or orange yellow, not black. This fact was noted by Mertsching [12] (1889) who also observed a correlation between size and lightness of color for individual granules. Mandoul [13] (1903) found variations in the size of melanin granules associated with differences in complexion.

In normal skin, the melanin granules are discrete and not massed or packed against each other. Light, reflected from deeper tissues and from the epidermal cells which contain the pigment, passes through these melanin granules and emerges at the skin surface with a yellow component. Presumably, the granules absorb the complementary blue. In any case, their effect is not simply to darken the skin, but also to add enough yellow to produce brown in heavily pigmented skins. In lighter skins, the yellow component is not so obvious.

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mentation may be described as follows: (a) few cells of basal layer pigmented with few granules—blonds, (b) more cells containing more granules—brunettes, (c) a more or less complete basal layer of cells with many and very many melanic granules (mulattos), (d) the cells of basal layer packed and distended with pigment granules; the cells of the more superficial layer also with very many granules."

9. Davenport, C. B.: Heredity of Skin Color in Negro-White Crosses, Washington, Carnegie Institute Publication, no. 188, 1913.

10. Todd, T. W., and Van Gorder, L.: The Quantitative Determination of Black Pigmentation in the Skin of the American Negro, Am. J. Phys. Anthrop. **4**:239-260 (July-Sept.) 1921.

11. Vörner, H.: Beitrag zur Kenntnis des Pigmentes, Dermat. Ztschr. **12**: 379-387, 1905; Beitrag zur Kenntnis des Pigmentes in Erganzung zu dem gleichlautendem Artikel, ibid. **12**:499-501, 1905.

12. Mertsching: Histologische Studien über Keratohyalin und Pigment, Arch. f. path. Anat. **116**:484-516, 1889.

13. Mandoul (reference 5, page 317).

Whenever the epidermis is unpigmented and melanin pigment granules, packed closely, occur in the deeper integument, bluish or blue-gray effects are to be expected. It is not clear just how thick the unpigmented tissue must be, but in thin skin it would seem that most of the epidermis, at least, should be without pigment. The masses or groups of melanin granules must be large enough to appear black under the microscope or nearly so (fig. 3, melanophores).

The production of blue effects under such circumstances has been generally interpreted by different authors as due to a turbid medium overlying a region in which melanin pigment occurs in considerable amounts. The color of blue feathers was explained by Haecker [14] (1890) as due to such a combination of structure and pigment. He made use of the Lord Rayleigh theory of the cause of a blue sky. Adachi [15] (1903) employed the same theory in discussing the blue effect in sacral patch. It has been used in explaining blue eyes, and it has been employed by others (Mandoul, 1903, Camichel and Mandoul,[16] 1901) in discussions of blue integumental effects.

The turbid medium theory involves the assumption that there are particles in a medium with a smaller index of refraction; or, vice versa, the medium may have a high index of refraction, with exceedingly small cavities filled with air or any gas of less refractive power. The particles or the cavities must be small, compared with the shorter light waves.

The existence of such cavities in the form of minute canals was demonstrated experimentally by Haecker. Further evidence concerning their existence and origin was obtained by Kniesche [17] (1914). Such an arrangement has not been demonstrated to my knowledge in the skin or in the iris. The structure of any tissue is complex enough, however, to warrant the assumption that it may act as a turbid medium. It is necessary to have a dark background, however, to prevent swamping of the weak blue effect by light reflected from deeper tissues.

Melanin pigment may occur in the corium with or without a normal epidermal pigmentation. There is considerable variation in the distribution of melanin in different regions of the body, according to

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14. Haecker, V.: Ueber die Farben der Vogelfedern, Arch. f. mikr. Anat. **35**:68-87, 1890.

15. Adachi, B.: Hautpigment beim Menschen und bei den Affen, Ztschr. f. Morphl. u. Anthrop. **6**:1-131, 1903.

16. Camichel and Mandoul: Des colorations bleue et verte de la peau des vertebres, Compt. rend. Acad. d. sc. **133**:826-828, 1901.

17. Kniesche: Ueber die Farben der Vogelfedern: I. Die Grünfärbung auf Grundlage der Blaustruktur, Zool. Jahrb. Abt. Anat. **38**:327-356, 1914; II. Die Färbung der Columba livia nebst Beobachtunen ueber die mechanischen Bauverhältnisse der Vogelfedern, ibid. **38**:357-426, 1914.

Breul [18] (1896), who described the occurrence of melanin in the skin of various parts of the body and for different complexions. He found spots in the axilla in a brunette (his case 1), where a rich corium pigmentation was accompanied by a total lack of epidermal pigment. Elsewhere, however, the corium contained only occasional pigment cells.

The literature of dermatology contains many instances in which a yellow component was lacking and a bluish cast appeared. Most of these are cases of sacral patch ("Mongol fleck," "taches bleues").

Various causes may exist for blue skin. A bit of black material in the corium will produce a bluish effect. Often the blue is illusory, for one is so accustomed to a yellow component that a gray without a yellow component seems bluish by contrast. Use of the color wheel brings out this point strikingly. Combinations of black and white disks only, in the color wheel, give grays which are identical with colors often called blue-gray.

In this paper, the attempt is not made to distinguish between neutral grays, which may have been called blue by the writers, and grays with a real blue component, because the cases are not available for critical examination.

In a number of cases described in the literature, some of which are mentioned by Mandoul [19] (1903), foreign material has been deposited in the dermis. Thus, frequent use of a dirty hypodermic needle by morphine addicts has been responsible for bluish spots or specks in the skin (Moutard-Martin,[20] 1897; Gottheil,[21] 1908; Cedercreutz,[22] (1917). Galliard and Lasnier [23] (1903) mention a case in which black carbon particles were found in the deep dermis, resulting in a blue color. Cyanotic skin, in cases of morbus coeruleus, owes its blue to blood changes, which are outside the province of this paper.

Blue skin has sometimes been found to be infested with parasites, notably pediculosis pubi in the skin of the pubis (Von During,[24] 1901;

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18. Breul, L.: Ueber die Vertheilung des Hautpigments bei verschiedenen Menschenrassen, Jena, Morphol. Arb. **6**:691-720, 1896.

19. Mandoul (reference 5, pp. 328-330).

20. Moutard-Martin, R.: Pigmentation bleue chez une morphinomane névropathe et syphilitique, Gaz. d. hôp., Paris **70**:706-709, 1897.

21. Gottheil, W. S.: Macular Atrophic Blue Pigmentation of Arms and Legs; Presented for Diagnosis, J. Cutan. Dis. **26**:281, 1908.

22. Cedercreutz, A.: Hudakomma bestaende af symmetriskt grupperade, talrika sma blapigmenterade flackar, lokaliserade till extremiteterna och till brostet (Skin disease, manifested by symmetrically grouped, numerous small blue macules on the extremities and chest [in a morphine addict]), Finska läk.—sällsk, handl. **59**:1454-1458, 1917.

23. Galliard, L., and Lasnier: Pigmentation bleue, en macules innombrables, des cuisses et des bras, apres dix annees de morphenomanie, Bull. et mém. Soc. méd. d. hôp. de Paris **25**:903-905, 1903.

24. Von During, E.: Hautpigment und Pigmentanomalien, Deutsche Klinik **10**:315-334, 1901.

Jamieson,[25] 1889; Oppenheim,[26] 1901; Bowditch,[27] 1895). The pigmented parasites buried deep in the skin may take the place of a corium pigmentation.

Of greater interest are cases due not to any foreign material but to pigmented anomalies as, for instance, the curious light blue patch which occurs sometimes in babies, especially in the Mongolian races. This has already been referred to as sacral patch, so called because it occurs characteristically in the sacral region. This was studied and described carefully by Adachi[28] (1902-1903) who found a corium pigmentation. Unfortunately, articles on abnormal pigmentation do not usually include any histologic details. Furthermore, many cases of bluish or slate colored skin have probably been overlooked, even by medical men.

A case of bluish skin on the face, with corium pigmentation, has been described by Grouven[29] (1901). Riehl[30] mentions cases with a gray "schimmer" and corium pigmentation, which probably belong in this category.

The case of "Blue Mary" described by Abbott[31] (1900) is of unusual interest. In this woman the skin of the face, neck and hands was "dark bluish or slaty in color." There was more or less fibrosis of all organs except the kidneys, with hemosiderosis. A heavy pigmentation of the connective tissues in the liver and pancreas was found, and there was a "fairly advanced chronic interstitial pancreatitis." The author was struck with the "surprisingly little microscopical evidence of pigment" in the skin. All that could be observed were a few golden brown granules in some large irregularly-shaped cells, situated in the connective tissue of the dermis, a little below the malpighian layer.

Lewin[32] (1883) described a case of Addison's disease with bluish black stripes on the hips and entire anterior surface of the body. The

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25. Jamieson, W. A.: On Some of the Rarer Effects of Pediculi, Brit. J. Dermat., 1889, pp. 321-327.

26. Oppenheim, M.: Ueber einen vom Pediculus pubis gebildeten Farbstoff, Arch. f. Dermat. u. Syph. **57**:233, 1901; abstr., Brit. J. Dermat., 1902, p. 74.

27. Bowditch, V. Y.: Observations upon Cases Having the So-Called "Taches Bleuatres" in the City Hospital, M. & Surg. Rep., Boston City Hosp. **6**:55-59, 1895.

28. Adachi, B.: Hautpigment beim Menschen und bei den Affen, Anat. Anz. **21**:16-18, 1902; (footnote 15).

29. Grouven: Ein Fall von ungewohnlicher Hyperpigmentation des Gesichts, Deutsche med. Wchnschr. **27**:235-236, 1901.

30. Riehl, G.: Ueber eine eigenartige Melanose, Wein. klin. Wchnschr. **30**: 780-781, 1917.

31. Abbott, Maude E.: Pigmentation Cirrhosis of the Liver in a Case of Haemochromatosis, J. Path. & Bact. **7**:55-70, 1901.

32. Lewin, G.: Ueber Morbus Addisonii mit besonderer Berücksichtigung der eigenthumlichen Pigmentation der Haut, Charité-Ann. **10**:630-726, 1883.

skin was bronze otherwise. He also noted several cases with dark gray skin. Histologic details were not given.

Blue skin was discussed by Von Luschan [33] (1916), who speaks of a bluish "unterton" in the skin, especially in the dark races. He recognized the relation of a combination of unpigmented epidermis with pigment below, to the production of a bluish effect. He considered it an interference phenomenon.

A case of abnormal pigmentation in which the color was a "peculiar slate-grey" was described by Sequira [34] (1904). The color was found in the mucous membranes as well as in the skin. The author says that the "Pigment was excessive in the normal situations, being well developed in the rete, and particularly around the sweat and sebacous glands."

Blue skin, associated with a melanotic sarcoma, has been described by Stowers [35] (1893) and Taylor [36] (1875). Two cases of blue skin were described by Dalchi and Fouquet (1903). In one of these, an alcohol soluble blue substance was found.

Abnormal pigmentations in the corium were recognized by Post [37] (1894). He says that much pigment occurs in both the epidermis and the corium in lentigo. A variable pigmentation was described for both epidermis and corium in nevus. One case presented a completely pigment-free epidermis. The corium in some cases showed a layer of pigment cells near the epidermis, the processes of which formed a network. In a case of melanosarcoma, pigment cells occurred in the corium near the epidermis. Post studied the skin in two cases of Addison's disease. There was an increased corium pigmentation in the scrotal skin with a variable amount of epidermal pigment. Only a limited pigmentation could be found in the basal cells. The corium papillae were richly pigmented. Conspicuous pigment masses, with granules of different size, occurred in the vicinity of the blood vessels.

Other writers who have described an unusual amount of pigment in the corium of the skin but who do not mention a blue color are Gussenbauer [38] (1875), Hallopeau,[39] Jeanselme and Meslay (1893),

33. Von Luschan, F.: Ueber Haut farbentalfen, Ztschr. f. Ethnol. **48**:402-406, 1916.

34. Sequira, J. H.: Case of "Peculiar Slate-Grey Pigmentation of the Skin and Mucous Membranes," Brit. J. Dermat. **16**:348-349, 1904.

35. Stowers, J. H.: Case of Melantotic Sarcoma of Left Ear, Brit. J. Dermat. **5**:305-307, 1893.

36. Taylor: A Case of Idiopathic Multiple Pigment; Sarcoma of the Skin, Arch. of Dermat. **1**:307-309, 1875.

37. Post, H.: Ueber normale und pathologische Pigmentirung der Oberhautgebilde, Arch. f. path. Anat. **135**:479-513, 1894.

38. Gussenbauer, C.: Ueber die Pigmentbildung in melanotischen Sarcomen und einfachen Melanomen der Haut, Arch. f. path. Anat. **63**:322-355, 1875.

39. Hallopeau, H.; Jeanselme, E., and Meslay: Sur un cas de dysystrophie papillaire et pigmentaire (acanthosis nigricans), Ann. de dermat. et syph. **4**:876-883, 1893; Bull. Soc. franç. de dermat. et syph. **4**:432-439, 1893.

Kingery [40] (1918), Variot [41] (1887), Pförringer [42] (1900), Wende and Bauchus [43] (1919), Gaston and Emery (1898) and Wieder [44] (1926).

Adachi found two kinds of pigment cells in the corium of the skin. A layer of small melanophores was observed in the superficial corium, and there was a layer of larger melanphores in the deep corium. The corium of the sacral patch had large pigment cells which extended from one half to two thirds of its depth. These he described and figured as usually spindle-shaped but sometimes stellate. The papillary layer contained very little pigment.

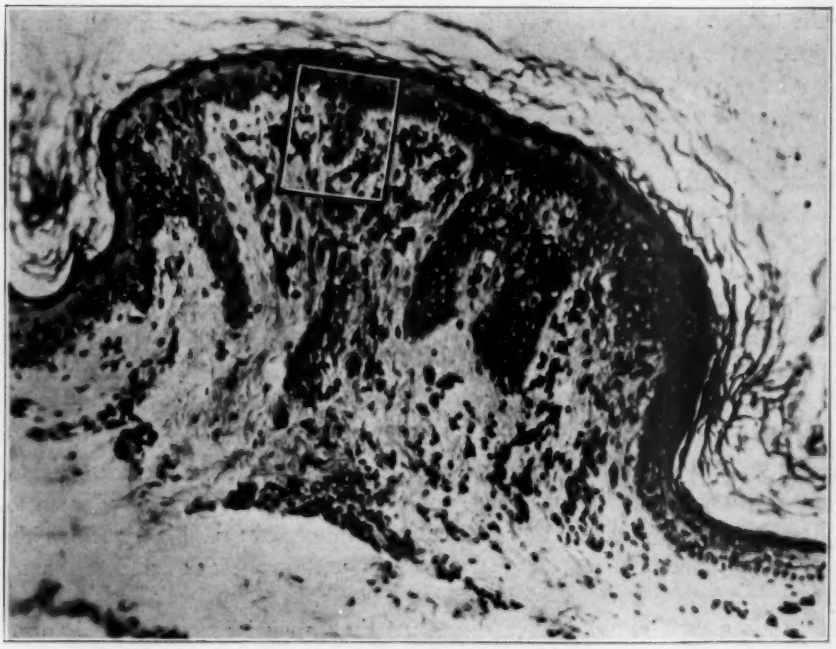

Fig. 1.—Photomicrograph of section of skin from the scrotum; the region enclosed by the rectangle is shown in figure 2. × 170.

40. Kingery, L. B.: Schamberg's Progressive Pigmentary Dermatosis; Report of a Case with Histologic Study, J. Cutan. Dis. **36**:166-172, 1918.

41. Variot, G.: Lesions de la peau dans la mélanodermie congénitali et dans le naevus pigmentaire circonscrit, Compt. rend. Soc. de biol., series 8, **4**:257-258, 1887.

42. Pförringer: Zur Entstehung des Hautpigments bei Morbus Addison, Centralbl. f. allg. Pathol. u. path. Anat. **11**:1-7, 1900.

43. Wende, G. W., and Bauchus, H. H.: A Hitherto Undescribed Generalized Pigmentation of the Skin Appearing in Infancy in Brother and Sister, J. Cutan. Dis. **37**:685-701, 1919.

44. Wieder, L. M.: Acanthosis Nigricans: Juvenile Type, J. A. M. A. **87**: 1964-1969 (Dec. 11) 1926.

Prof. R. T. Shields of Shantung Christian University, Shantung, China, supplied me with some sacral patch skin to study. My observations confirm the description of Adachi, and I have nothing new to add.

Fig. 2.—Drawing of region indicated by rectangular outline in figure 1. Zeiss, apoch. obj. 2 mm., comp. oc. 12. Camera lucida. × 1,000.

In the case mentioned in the first paragraph of this paper, melainin pigment occurred in the papillary layer of the corium as shown in figures 1 to 3. These illustrations were prepared from a slide of scrotal skin given to me by Professor Warthin. This section was used as it was especially suitable for both photomicrographs and drawings. However, it represents fairly the condition in which a bluish cast to the

skin was observed. This slide shows a still greater number of melanophores in the corium than are to be seen in my preparations made three years earlier. Also, there are more melanin granules in the epidermis than in my material. Warthin, Crane and Jackson [45] (1924), in their discussion of the same case, noted a similar distribution of pigment in other regions.

The pigment in the epidermis is exceedingly scanty, and it occurs in only a small proportion of the rete cells. The granules are much smaller, and consequently they are lighter in color than in the corium. The general appearance (fig. 11, Warthin, Crane and Jackson) is like that shown in figure 1.

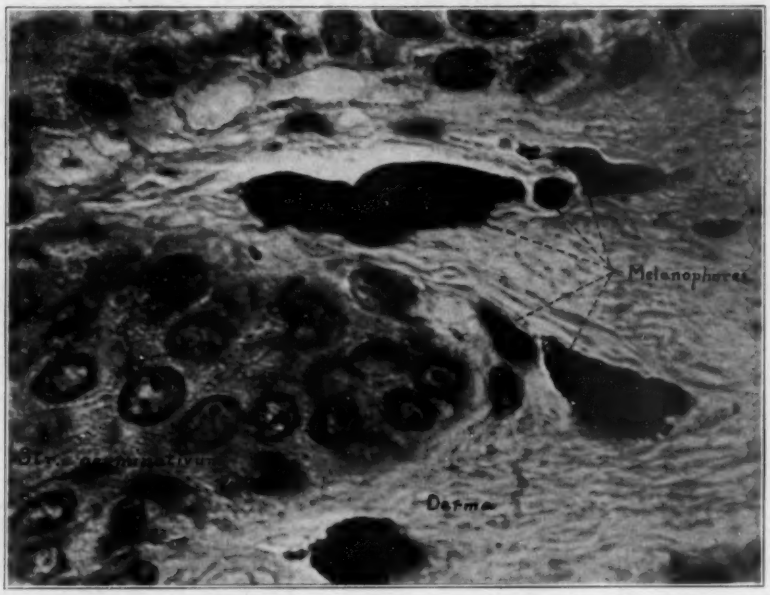

Fig. 3.—Photomicrograph of region similar to that shown in figure 2. × 1,000.

SUMMARY

In normal human skin, a yellow component is contributed by discrete melanin granules in the epidermis. When the epidermis contains little or no melanin pigment and there is much melanin packed closely in masses in the corium, a bluish cast to the skin may be expected. Many cases of Addison's disease show an increased corium pigmentation. Some of these have little or no pigment in the epidermis, and the skin then has a bluish cast. In such cases, the melanophores occur largely or entirely in the papillae of the corium.

45. Warthin, Crane and Jackson (footnote 2, p. 158).—"The blue-black areas corresponded to the heavy pigmentation of the chromatophores in the corium, while the rete showed little or no pigmentation."

SO-CALLED CHRONIC APPENDICITIS*

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During the last decade it has become routine to remove the appendix when the abdomen has been opened because of some other condition. During this same period, the term chronic appendicitis has gradually crept into usage, this designation being applied in many instances when the past history does not even remotely suggest a previous acute attack. It is the object of the present paper to consider the so-called "chronic appendicitis" from the etiologic and anatomic standpoint.

The terms "acute" and "chronic" have a definite meaning when applied to clinical conditions in the domain of internal medicine. These definitions have, however, come to mean something different when applied to surgical conditions. It is essential, therefore, to have a clear understanding of just what these terms mean. From the standpoint of internal medicine, "acute" is taken to mean occurring suddenly as, for example, acute rheumatic fever; while "chronic" is indicative of a longer duration as, for example, chronic arthritis. Surgically speaking, "acute" carries the same meaning as in the field of internal medicine, but "chronic" has come to mean a lesion the duration of which has been sufficient to permit fibrotic changes to occur in the tissue. This distinction is made, not by the clinician, but by the pathologist, who, seeing fibrosis accompanied by infiltration of wandering cells in a given tissue, calls the change "chronic" instead of using the term "productive." The extent and degree of fibrosis does not of necessity bear a direct relationship to the duration of the condition. Fibrosis is dependent either on the nature of the toxic substance or on interference with the blood and nerve supply of the part. I have repeatedly seen marked fibrosis and cellular infiltration develop within two weeks after the experimental introduction of an irritant into the tissues, and two weeks cannot be considered long from the standpoint of chronicity. Therefore, the terms used should be "acute" and "productive." The degree of the acute inflammation may be more exactly designated as catarrhal or mild, and suppurative or severe, while productive changes may be described as slight, moderate or marked.

A second point on which an agreement has still to be reached is the histology of a normal appendix. It may seem a rather simple task to establish the normal histology, but an actual experience with a group of histologists will soon convince one that while there may be unity on the

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histology of the normal liver or kidney, this unity disappears when the appendix is discussed. I have adopted as the normal the appearance of the appendix of infants between the ages of 4 and 12 months.

A series of twenty-seven appendixes from infants show the following rather uniform histology. The serosa except in the region of the meso-appendix is delicate. Its outer surface is covered by a layer of endothelium from one to three rows deep. Beneath this are a few fibrils of connective tissue which do not show any nuclei or which show them at wide intervals. Wandering cells and blood vessels are absent. In the region of the meso-appendix the layer is thicker, blood vessels may be demonstrated in certain planes of section, and occasionally there is a scanty infiltration with wandering cells. Proceeding from without inward, the next layer is smooth muscle with the fibers arranged more or less along the long axis of the organ. In this layer are most of the cells of the sympathetic nerve system ganglion of Auerbach. These cell groups contain from four to seven or eight cells, and in proper plane the collected fibers may be demonstrated emerging from one or the other end of the group. On cross section they appear somewhat circular. The ganglions do not show round cell infiltration. The next layer is again a muscular layer with the fibers in general arranged circularly. Occasionally, cells of Auerbach's plexus are found in this layer. Proceeding inward the next layer is the submucous connective tissue, and since the lesion to be described subsequently initiates here, it will be described in considerable detail.

At its outer ring, the submucous layer is not sharply defined from the inner ring of muscle, little bundles of muscle penetrating it for a slight distance in an irregular fashion. Its cross section is approximately one half the width of the inner muscle layer. The inner ring of the submucous coat presents as a line with peaks, the peaks fitting between the lymphoid follicles. The ganglion cells of Meissner are found in two areas, one directly adjacent to the inner layers of muscle, the other group between the lymph follicles. The submucous connective tissue is relatively noncellular, and does not show any round cell infiltration. Except for occasional small areas directly about the blood vessels, areolar tissue is not present.

The lymphoid zone of the appendix consists of a number of discrete follicles which rest below on the submucous connective tissue as a sort of cradle, and which above or toward the tube lumen come in contact with the somewhat poorly developed muscularis mucosa. Between the follicles there are a few scattered lymphoid cells. The structure of the follicle is typically that of lymphoid follicles in other portions of the body.

The mucosa consists of simple tubular glands of uniform size and form which are evenly spaced. These glands are lined by a single layer of columnar epithelium, many of the cells being filled with the products

of secretion, a mucoid material. Supporting these glands is a relatively dense stroma in which there are many round cells, and acting as a basement membrane for the layer is a poorly developed muscularis mucosa.

The histologic material on which the present paper is based consists of 3,214 appendixes. The anatomic diagnoses were as follows:

Tuberculosis	21
Carcinoma	12
Lipoma	1
Polyp	1
Diverticulum	1
Acute suppurative appendicitis	1,275
Acute catarrhal appendicitis	437
Productive appendicitis	1,374

Productive inflammation of the appendix occurred in 42 per cent of the specimens. Ribbert found this condition in 25 per cent of 400 specimens; excluding those from patients under 20 years the percentage rose to 32 per cent, and excluding those from patients under 50 years the incidence rose to 50 per cent. Zuckerland observed more or less obliteration in 23.7 per cent of 232 specimens. The condition has been found to occur at any time after the fifth year of life.

A general survey of the organ indicates that the first changes occur in the submucosa which becomes thickened and infiltrated with round cells, and shows areas of areolar tissue. The extent of these changes varies not alone in different appendixes, but also in different portions of the organ. The cellular infiltration gradually increases to a maximum when the mucosa commences to atrophy and the epithelial glands become shorter, and the shortening continues until the lumen is lined by a single layer of columnar epithelium. At about the time the epithelium has atrophied to a single layer, the lymphoid follicles commence to atrophy, and as the last of the epithelium atrophies, the lymphoid elements also gradually disappear. In the place of the atrophied tissues there is an increase in the thickness of the submucous coat, and finally the lumen of the organ is completely filled in. Slowly the round cell infiltration disappears and the appendix is represented by a central core of more or less hyaline connective tissue surrounded by the double muscle layer. While these changes are going on in the inner portions of the organ the muscular layers show little or no change. The serosa becomes more or less thickened and shows new cell and blood vessel formation as well as wandering cell infiltration.

A more detailed study of the various tissue layers at various stages of the process indicates a possible etiology for this productive reaction and atrophy. The lesions commence at the tip and gradually proceed toward the cecum. The entire organ is usually not affected to the point

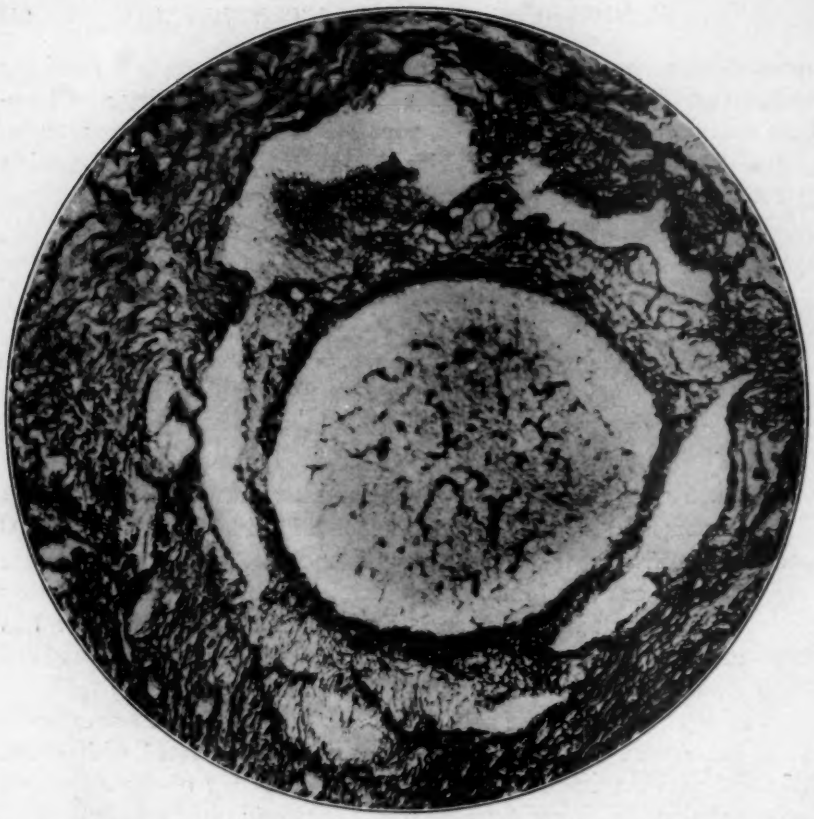

Fig. 1.—Bielchowsky stain, showing framework surrounding lymph follicle and illustrating why these elements are the last to atrophy. × 200.

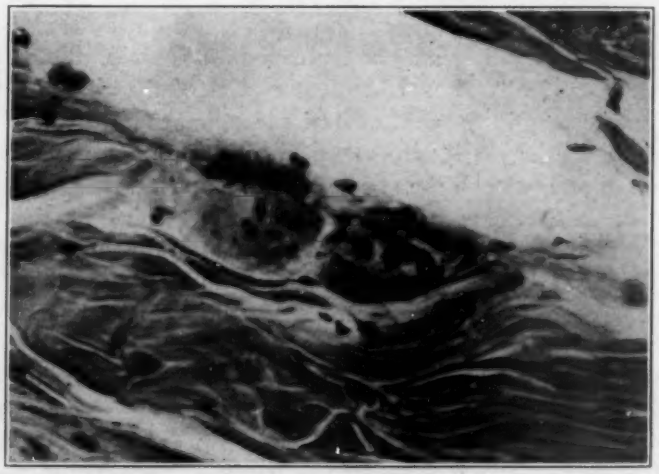

Fig. 2.—Normal ganglion cells of Meissner. × 250.

of obliteration, the gross changes being evident usually not beyond the middle. However, the microscopic changes about to be described can be found up to the cecal end.

The first deviation from the normal is that some of the cells of Meissner's ganglion are surrounded by a small collar of round cells. In the early lesions only a few of the ganglions are involved, but gradually the number involved increases and the round cell infiltration becomes more marked until the ganglion may be completely buried in a mass of round cells. The round cell infiltration, having attained a maximum, slowly recedes as the generalized fibrosis increases; and in the terminal stage the more or less damaged ganglion is found embedded in dense scar tissue which surrounds the nerve cells in a circular fashion exerting

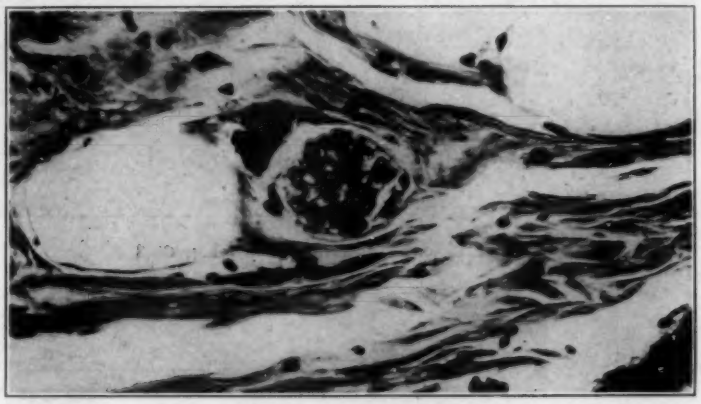

Fig. 3.—Early stage of round cell infiltration of ganglion cells of Meissner. × 250.

evident pressure, as is shown by the close proximity of the connective tissue and the distortion of the ganglion group.

During this period, constant changes do not take place in the blood vessels until fibrosis is far advanced, when in many, but not in all, instances there is a varying degree of sclerosis.

Such changes as are observed in the Meissner group are not seen in the ganglion cells of Auerbach; occasionally they show marked vacuolization, and in general they appear to be larger than in the normal appendix.

The serosa during the process may or may not become thickened, slightly or excessively; when such thickening is present, it is practically always due to new fibers, wandering cells and blood vessels, and not to edema.

The frequency with which the individual changes occur is shown in the accompanying tabulation. Of 77 consecutive specimens the serosa was normal in 28, slightly thickened in 27, moderately thickened in 16

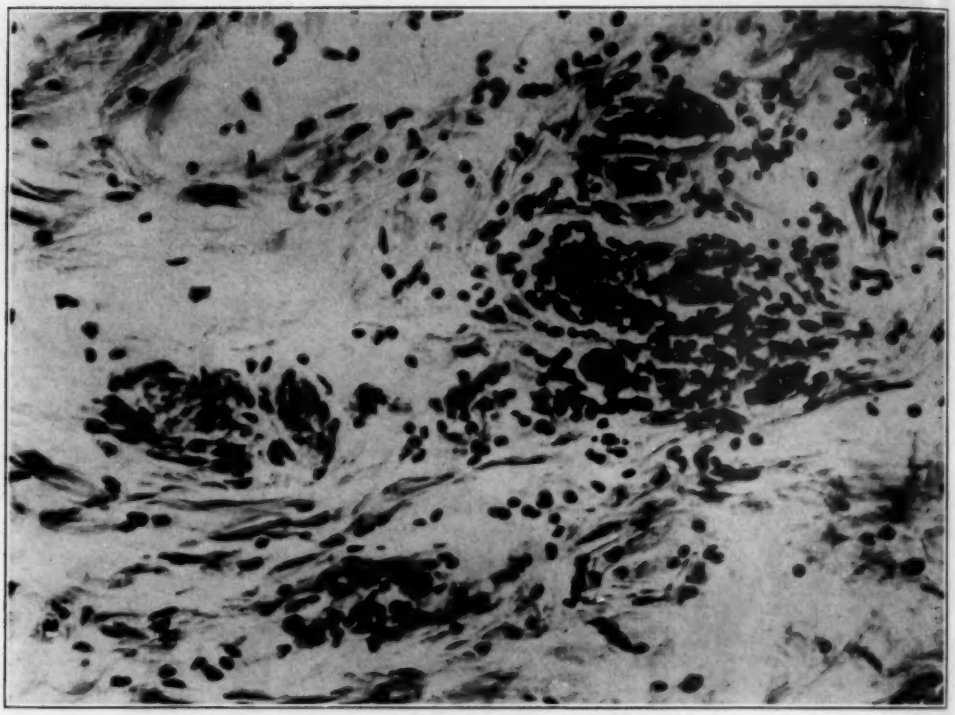

Fig. 4.—Midstage of round cell infiltration about group of ganglion cells. × 150.

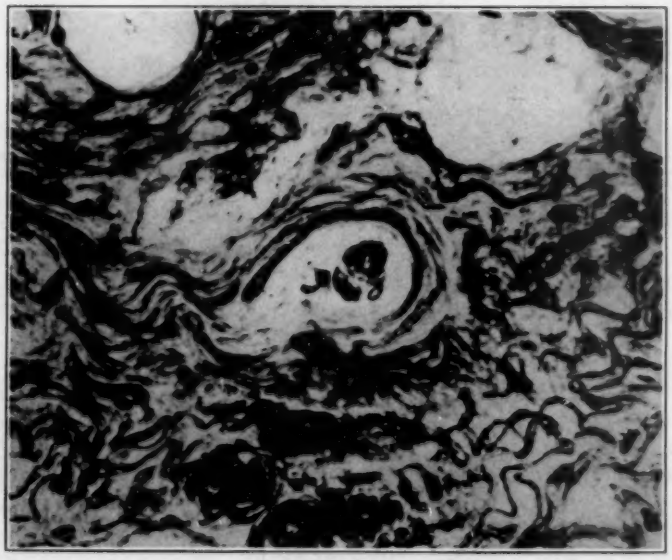

Fig. 5.—Terminal stage of fibrosis; Bielchowsky stain, showing compression of ganglion cell group.

and markedly thickened in 6. In 68 consecutive specimens the muscular coats were normal in 58 and fibrosed to varying degrees in 10. In 71 consecutive appendixes, the submucous layer was normal in 2, slightly thickened in 7, moderately thickened in 35 and markedly thickened in 27. Of these 71 specimens 45 showed more or less extensive fat deposits in the submucous layer and 60 presented a lesser or greater degree of cellular infiltration. Of 77 consecutive specimens, the lymphoid tissue was normal in 42, hyperplastic in 15, hypoplastic in 16 and completely atrophic in 4. The mucosa in 76 consecutive appendixes was normal in 62, slightly atrophic in 5 and completely atrophic in 9.

The relation of the productive changes which have been described to the incidence of acute inflammatory attacks is of interest. Of 250 consecutive appendixes in which acute inflammatory changes were found, productive changes were also observed in thirty-seven. Apparently, the productive changes but slightly increase the susceptibility of the organ to an acute suppurative inflammation. Of the thirty-seven, twenty-four were classed as catarrhal, i. e., mild in character. From these figures it would appear that if an acute inflammation does occur in an organ in which productive changes are going on, the attack, when viewed from the histologic appearance, is more likely to be mild than severe. However, histologic appearances do not always run parallel with clinical symptoms.

The relation of productive changes in the appendix to lesions in other intra-abdominal viscera is also of importance. Of 275 consecutive cases in which the appendix was the site of productive inflammation, the gallbladder was removed at the same time in twenty-five. Of these gallbladders, eight contained calculi and the remainder (seventeen) presented the histologic appearance of a productive inflammation of greater or lesser severity. Sections taken from the neck of the viscus disclosed areas of infiltration about the ganglion cells, similar to those observed in the appendix.

The present series does not give any data on the relationship of gastric ulcer to a lesion of the productive type in the appendix. It is of interest, however, to recall that a number of observers have reported on lesions of the sympathetic nerve system in gastric ulcer.

COMMENT

The clinical picture of so-called chronic appendicitis varies. Occasionally, with a past history of an attack of acute inflammation in the right lower abdominal quadrant, but much more often without such history, the patient recites an ill-defined series of complaints. There may or may not be tenderness or discomfort of varying degree over the general region of the appendix. Associated with this are vague symptoms referable to the stomach, and these symptoms range from

distress with gas after eating to acute attacks of pain after eating. Such patients often complain of constipation which, on analysis, is usually found to be of the spastic type. Physical examination with direct reference to the complaint elicits, on pressure, pain over the entire large intestine as well as along the course of the iliac vessels. Most of the patients can be placed in what the endocrinologist terms the autonomic type. Laboratory examinations seldom show any characteristic variation from the normal. Roentgenographic examination is slightly more instructive, showing a picture which can be interpreted in its broadest sense as the result of proliferative processes which extend to the serosa of either appendix or gallbladder, thus either producing distortion of the organ itself or by adhesions causing distortion of adjacent organs, such as the duodenal cap. Not infrequently in such pictures, there are evidences of spasm either in the stomach or in the large intestine. The further clinical observation that many of the patients whose cases are thus diagnosed are not cured and in many instances not even improved after operation is indicative of the fact that the lesion itself has not been corrected by the surgical procedure advocated. These variations in symptomalogy and the sometimes poor results of surgery could be explained easily on the basis of the anatomic changes described in the previous paragraphs.

The condition of so-called chronic appendicitis is in reality a productive inflammation of that organ produced by a lesion of the sympathetic nerve system. This lesion is not restricted to the appendix alone. It is also found in so-called chronic cholecystitis both with and without stones. The lesion, therefore, is probably general to the splanchnic sympathetic nervous system. In the appendix the ganglion cell lesions occur first and are followed by a fibrosis. The nerve lesions would thus explain reflex gastric symptoms, the attacks of spasm in the gastro-intestinal tract and the pain. They would also explain why simple removal of either the appendix or the gallbladder, or of both, is in many instances insufficient to relieve the symptoms.

It is not the object of the present report to decry the removal of the appendix with productive changes; such removal, however, should be reserved for cases in which the pain remains fairly well localized, and in which suitable medical treatment does not afford relief. Removal of the appendix when the abdomen is opened for some other condition does not come under consideration.

SUMMARY

In so-called chronic appendicitis a productive fibrosis occurs that involves especially Meissner's ganglions and that may be part of a productive process involving other abdominal structures.

HISTOLOGIC STUDIES ON THE FAT CONTENT OF THE NORMAL HUMAN THYROID*

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CHICAGO

Lipoid droplets are constantly found in the epithelial cells of the human thyroid after the first year of life. In early childhood the droplets are scanty and fine, increasing gradually in number and size until at the time of puberty they form a continuous granular zone along the internal margin of the vesicular epithelium. What may influence the lipoid content of the thyroid in later life is not yet definitely known. The stage of nutrition does not seem to be of any importance (Arndt,[1] Haeberli[2]). On the other hand, age (Erdheim,[3] Haeberli) and certain diseases (Buscaino,[4] Parhon and Stocker,[5] and Fukushe and Eguchi[6]) are believed to increase the amount of visible fat in the thyroid epithelium.

Little attention so far has been given to the question whether the lipoid droplets of the thyroid have anything to do with the secretory activity of this gland. Do the fat droplets merely pile up in the cells as waste products of their metabolism without being excreted, similar to the pigment granules in the ganglion cells of the brain? Or are they excreted into the vessels surrounding the vesicles or into the colloid? In the later case, which seems to be more likely because of their localization near the internal surface of the cells, do they take part in the formation of the vesicular content?

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*From the Department of Pathology, College of Medicine, University of Illinois.

1. Arndt: Ueber die morphologisch nachweisbaren Lipoide in Epithelkoerperchen und Schilddruese des Menschen, Beitr. z. path. Anat. u. z. allg. Pathol. **72**:517, 1924.

2. Haeberli: Ueber die morphologisch nachweisbaren Fettsubstanzen und die Oxydasereaktion in der menschlichen Thyroidea, Virchows Arch. f. path. Anat. **221**:333, 1916.

3. Erdheim: Zur normalen und pathologischen Histologie der Glandula thyroidea, parathyroidea und Hypophysis, Beitr. z. path. Anat. u. z. allg. Pathol. **33**:158, 1903.

4. Buscaino: Rivista di Pathologia nervosa e mentale, Firenze 1914, reviewed in Vercelli: Studies of the Thyroid and Its Qualitative Variations, Endocrinology **4**:88, 1920.

5. Parhon and Stocker: Sur la Frequence relative des granulations lipoides dans les cellules thyroidiennes dans differents cas pathologique, Bull. et mém. Soc. neurol. psychiat. et psychol. de Jassy **2**:154, 1921.

6. Fukushe and Eguchi: Beziehungen der regressiven Veraenderunger der Schilddruese zu den verschiedenen Krankheiten, Tr. Japanese Path. Soc. Tokyo **13**:138, 1923.

According to Lobenhofer,[7] colloid is a mixture of different substances one of which is of a fatlike nature. Haeberli, Arndt, Buscaino and others mention the occurrence of fat in the colloid, which they thought was derived from desquamated and degenerated cells. Erdheim denies any connection between the lipoid granulation of the epithelium and secretory processes.

In the present communication I shall describe histologic pictures which indicate a secretion of lipoids through the vesicular epithelium into the lumen of vesicles. The microchemical reactions of these secretory products with the different fat stains will also be discussed. It is known today that these reactions do not allow definite statements as to the chemical composition of a given mixture of lipoids. Some of the stains, like the Fischler method for fatty acids, are not specific. However, certain conclusions may be drawn from the results obtained by the fat stains if one keeps in mind that the predominating fatty substance will obscure others present in minor quantities.

MATERIAL AND METHODS

The studies were carried out on seventy thyroid glands from persons varying in age from 22 hours to 86 years. Only fresh and apparently normal glands removed within a few hours after death were used. Great care was taken to avoid pressure and tearing during the dissecting. Thin slices of tissue were dropped immediately into a 10 per cent formalin and Caccio's mixture. The common fat staining methods (sudan III, nile blue sulphate, Lorrain-Smith, Caccio, Fischler) were used.

I. FAT CONTENT OF THE EPITHELIUM

All the thyroids except six (from children, aged 22 hours, 4 days, 5 days, 6 weeks, 3 months and 11 months, respectively) contained fat. There was little fat in the glands of nine children whose age was from 6 months to 13 years. The thyroid of a girl, aged 15 years, who died of acute encephalitis, showed a large number of fat droplets in the epithelial cells. In the other cases the amount of fat varied greatly, dependent not only on age but also on other conditions. Generally speaking, the glands rich in lipins were more common after the fortieth year than earlier. But even in very old people a thyroid with little fat was found occasionally. On the other hand, glands with much fat were not exceptional in persons under 30 years of age (table 1). Diseases do not seem to influence the fat content. Under the same pathologic conditions all possible grades of fat accumulations may be observed. Thus, of eleven cases of carcinoma three presented thyroids with little fat, two with medium amounts and five with large quantities.

7. Lobenhofer: Beitraege zur Lehre der Sekretion in der Struma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **20**:651, 1909.

In the thyroids of patients more than 40 years of age, large fat droplets from 5 to 8 microns in diameter are often found.

In the same thyroid and even in the same vesicle the individual epithelial cells show differences in the lipoid content. Cells with little fat border on cells crowded with it. I think that this phenomenon represents different stages in the segregation of the lipins.

First, fine, dustlike granules appear between the nucleus and the internal margins of the cells. The granules form rosettes, are insoluble in chloroform, are soluble in ether, alcohol and acetone and give the color reactions of neutral fat. They become more numerous later, they grow larger and their chemical nature changes. They are still soluble in ether, alcohol and acetone and are not double refracting, but they now stain bluish violet or deep blue with nile blue sulphate and deep gray or

TABLE 1.—*Lipoid Content of the Thyroid Epithelium in Different Ages*

Age	No Fat	Very Little Fat —Many Cells Free from It	Little Fat in the Form of Small Droplets in the Majority of the Cells	Much Fat in Droplets of Various Sizes	Most of the Epithelial Cells Crowded with Fat Droplets Which Often Fill the Entire Cell
0-11 months	5	2	0	0	0
1-10 years	0	4	1	0	0
11-20 years	0	3	1	1	0
21-30 years	0	1	3	2	9
31-40 years	0	4	4	3	0
41-50 years	0	2	4	4	3
51-60 years	0	1	3	4	3
61-70 years	0	1	1	5	2
71-85 years	0	1	1	1	0

black after the Lorrain-Smith Dietrich potassium bichromate-hematoxylin method (fig. 1). They give, therefore, the staining reactions of phosphatides. Similar results were obtained by Arndt.

In the glands of older persons, grayish brown pigment granules are found in addition to the fat droplets. Extracting the fat with alcohol often intensifies their color. Hueck supposes that these pigments are lipofuscin. They were observed by Erdheim, Arndt, Haeberli and others.

The droplets that stain black with the Lorrain-Smith-Dietrich potassium bichromate-hematoxylin method are ready to be discharged into the vesicular lumen. Varying numbers of droplets remain in the cells and change once more their reactions. They become insoluble in alcohol and acetone but remain soluble in ether. They stain bright orange yellow with Caccio's sudan III. From these reactions it may be suggested that cephalin mixtures are now predominating. Also, the Caccio-positive droplets are finally discharged into the central lumen.

After the cell has given off its fat content the process of lipoid segregation starts again.

II. FAT CONTENT OF THE COLLOID

In the colloid the fat is found in three different forms. 1. It appears as small droplets, from 1 to 2 microns in diameter. The small droplets are suspended in spheroids which measure from 5 to 10 microns and do not take the fat stains. These spheroids have a greater affinity to the hematoxylin than the surrounding colloid. They are discernible only in hematoxylin stained frozen sections of glands fixed soon after death

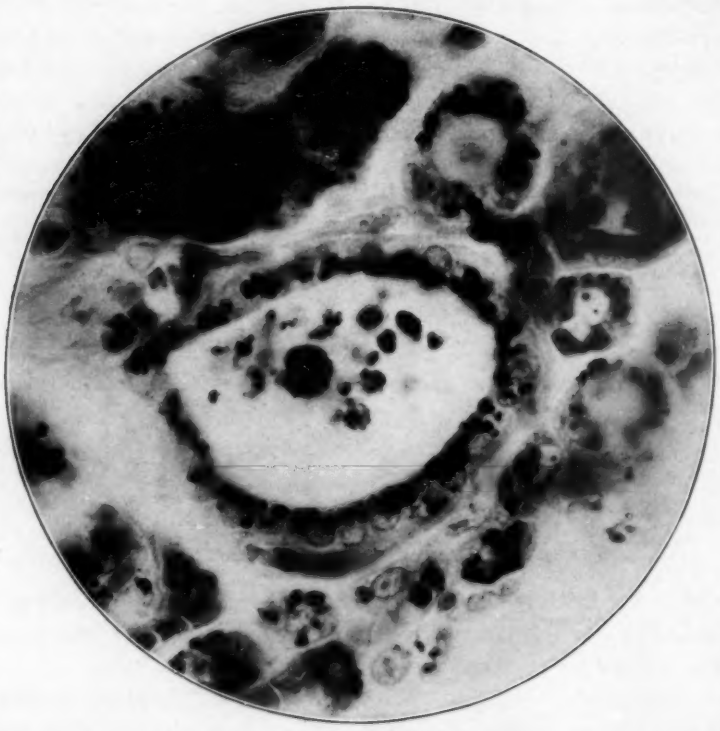

Fig. 1.—Thyroid, weighing 23 Gm., of a man, aged 65, who died from a carcinoma of the colon; in the center of the field is seen a vesicle, lined by cuboidal epithelium, which is filled with larger lipoid droplets; a few cells are free from fat; in the lumen are several spheroids with lipoid droplets and a group of larger drops. Frozen section, fixed with 10 per cent liquor formaldehydi. Lorrain-Smith-Dietrich stain and safranin.

with formalin. Other stains or fixing solutions or paraffin and celloidin embedding cause them to become more or less invisible. The fat droplets are excreted by the epithelial cells together with the spheroids.

The number of spheroids varies (comparison should be made in table 2). In some cases as many as from forty to seventy are found in

one vesicle. In other cases only a few are present. Also, the lipoid content of the single spheroid shows differences. Most of the spheroids contain from one to five droplets; some are filled with them and others may be found without any.

This type of lipoid secretion is seen during the whole life, starting with the first appearance of fat granules in the epithelial cells. The amount of fat in the colloid is parallel with that of the epithelium.

The spherical vacuoles with the fat droplets resemble the chromophobe secretion described by Wyss, Andersen, Key [8] and others. Key also mentions the presence of chromophile granules in the vacuoles. He believes that these granules are composed of lipins and proteins (liposomes). However, they are not identical with the droplets described previously, because they are scanty in the normal human thyroid while the latter are usually numerous.

TABLE 2.—*Lipoid Content of Colloid*

Age	Average Number of Spheroids per Vesicle	Average Number of Lipoid Granules per Spheroid	Average Number of Large Groups of Fat Droplets per Vesicle
0- 1 year	0	0	0
1-10 years	0.7	3.3	0
11-20 years	1.9	1.7	0.003
21-30 years	15	2.6	0.07
31-40 years	43	2.3	0.12
41-50 years	17	2.9	0.3
51-60 years	19	1.3	0.2
61-70 years	19	1.4	0.5
71-85 years	30	1.3	0.5

2. Large droplets from 4 to 8 microns in diameter arrange themselves in mulberry shaped groups and seem to be kept together by a thin capsule. They are insoluble in alcohol and acetone and dissolve with difficulty in ether. They stain black with the Lorrain-Smith method and often bright orange after Caccio. The groups of larger fat droplets are absent from the glands of younger persons (table 2). They become more numerous after the fortieth year of life. Their mode of excretion is by way of the simultaneous extrusion of the lipoid content by a number of adjacent epithelial cells.

3. Foamy cells filled with fat globules are found in the colloid. Their nuclei are often pyknotic. These cells occur after puberty in about half the cases. Their number, however, is usually small. In only 10 per cent of the thyroids were they more numerous. The fat in the cells has the same properties as the fat in the larger clusters.

8. Key, J. A.: The Secretion Antecedents and Mitochondria in Pathological Thyroids, Arch. Surg. **11**:254 (Aug.) 1925.

III. THE FAT CONTENT OF THE STROMA

The stroma of the thyroid often contains typical fat cells; however, they are less numerous than in the parathyroid. These fat cells were described by Peremeshko, Erdheim, Haeberli, Arndt, Key and others. In my material they were found in half of the thyroids examined. There were also observed in the interlobular septums and in the scanty connective tissue about the vesicles elongated and branched cells filled with small lipoid droplets, giving the same microchemical reactions as the fat in the epithelial cells and in the colloid. Occasionally such a cell is seen extending with its branches between the vesicular epithelium.

Cholesterol and cholesterolesters were not found in the stroma of normal thyroids.

A striking and interesting observation was made on the plasma of the smaller blood vessels. The plasma often stained a distinct orange yellow with sudan III. The reaction was most pronounced in the small veins of the interlobular septums without a muscular coat. It was also found in the smaller arteries and precapillaries and in the perivesicular capillaries—in the latter vessels if the plasma had separated from the column of blood cells. Treating the frozen sections with ether, alcohol and acetones caused the reaction to disappear. Chloroform did not have any effect. The plasma also seemed to have peculiar physical properties. It resembled a thick oily fluid which was more adherent to the vessel wall than usual and had retracted from the blood cells (fig. 2).

The staining of the plasma with sudan III was noticed in 43 per cent of the thyroids studied. In 20 per cent it was so marked that it resembled the pictures seen in lipemic diabetes and experimental hypercholesterinemia of herbivorous animals.

A constant relation did not exist between the intensity of the fat reaction of the plasma and the lipoid content of the epithelium. Frequently the thyroids with little fat in the epithelial cells showed a bright orange plasma.

The content of the lymph vessels remained unstained.

In other organs of the same cases an affinity of the plasma to sudan III was only seldom observed. If present it was much weaker and confined to a few vessels. In fifty-four autopsies I saw a staining of the plasma with sudan III three times in the kidney, three times in the lung, twice in the liver and once in the thymus, while it was very distinct in twenty-three thyroids. It was never present in the parathyroids, hypophysis or suprarenals.

That the taking of the fat dye by the plasma in the vessels of the thyroid was not due to a disintegration of the blood after death was shown by the fact that similar results were secured in glands removed during life. This local lipemia in the thyroid indicates an active lipoid metabolism of the organ and demands further, especially experimental, investigations.

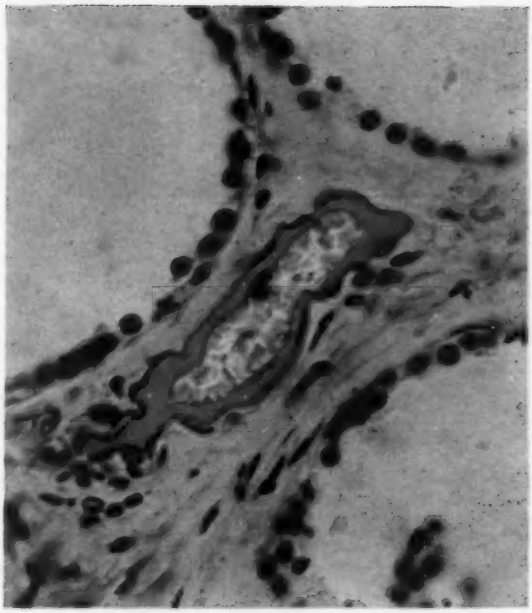

Fig. 2.—Thyroid, weighing 22 Gm., of a woman, aged 32; anatomic diagnosis: hemorrhage into the left central ganglion of the brain (died during an attack of eclampsia); a venule filled with sudanophile plasma which has retracted from the erythrocytes is seen; little fat is present in the low cuboidal epithelium of the vesicles. Frozen section fixed with 10 per cent liquor formaldehydi. Sudan III and hematoxylin.

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COMMENT

The morphology of the thyroid secretion has been studied by many investigators. Key, who recently reviewed the results obtained so far, states that utter lack of agreement still exists among the different authors. The constant occurrence of fatty substances in the thyroid epithelium and in the colloid, and the simple and reliable methods of demonstrating these substances in the tissues, allow one to follow more closely at least one part of the secretory activity of the thyroid.

Soon after the appearance of the first lipoid granules in the epithelial cells the process of excreting them into the lumen of the vesicles starts. The granules and droplets seem to be composed chiefly of mixtures of phospholipins. The epithelial cells discharge them suspended in larger drops of nonfatty material. The drops gradually lose their lipoid content, but they may still remain visible until they too become dissolved into the surrounding colloid.

In higher ages clusters of larger Caccio positive drops are found in the colloid. They disintegrate more slowly than the smaller droplets. Sometimes an epithelial cell filled with fat droplets becomes detached and enters the colloids; but this is not common in normal thyroids.

Normally, the rate of lipin excretion is slow; only occasionally is a cell found in the stage of discharging its content. However, if the epithelium is rich in fat this stage is frequently observed.

In another publication it will be shown that the picture of lipoid segregation and excretion is different in exophthalmic goiters, in some forms of adenoma and in malignant epithelial tumors of the thyroid.

The presence of lipoid carrying cells in the stroma of the thyroid indicates that some of the lipoid passes from the cells into the stroma. These cells no doubt are histiocytes, and their number increases with the age and the thickening of the interlobular septums. An excretion of lipoid granules into blood or lymph vessels was not found. However, the plasma in the smaller blood vessels often gave a distinct coloration with sudan III, suggesting that the blood that circulates about the vesicles is rich in fat.

Both clinical and experimental data are available which, in accordance with the microscopic observations, point toward some relation between the fat metabolism and the function of the thyroid. To quote some of them: Bing and Heckscher [9] found low values for the ether soluble substances of the blood in patients with exophthalmic goiter and high values in the blood of cretins. Epstein and Lande [10] mentioned a low

9. Bing and Heckscher: Der Fett-Cholesteringehalt des Blutes bei Patienten mit Morbus Basedow, Biochem. Ztschr. **158**:403, 1925. Heckscher: Ueber die Fett-Cholesterinmenge des Blutes bei Kretinen, ibid. **158**:422, 1925.

10. Epstein, A. A., and Lande, H.: The Relation of Cholesterol and Protein Deficiency to the Basal Metabolism, Arch. Int. Med. **30**:563 (Nov.) 1922.

cholesterol content of the blood in cases with high basal metabolism rates and a high content in those with low basal metabolism rates.

Martinez [11] recorded the presence of hypercholesterinemia in thyroparathyroidectomized dogs. E. Mellanby and M. Mellanby [12] described hypertrophy of the thyroid in puppies that were fed butter. It has long been known that feeding thyroid substance causes a marked loss of fat (Hoskins, Herring, and Cameron and Carmichael [13]). Arton [14] saw distinct changes in the content of the dog's liver on phospholipins after extirpation of the thyroid. Abelin, Goldener and Kobori [15] stated that diets rich in fat prevent the disappearance of the glycogen from the liver that otherwise takes place after the feeding of thyroid. They emphasize the great importance of fat for the action of the thyroid on metabolism.

SUMMARY

The lipoid droplets found in the epithelium of the thyroid gland in human beings are the products of the secretory activity of these cells. According to their staining reactions, they consist mainly of mixtures of phospholipins. They are discharged into the colloid where they are dissolved gradually.

The excretion of the lipins starts after the first year of life and increases with age. Also, in younger persons much fat is found occasionally in the epithelium and in the colloid. What may influence the intensity of the lipoid excretion cannot yet be definitely determined. Diseases do not seem to have any influence.

In 45 per cent of the thyroid glands distinct staining of the plasma of the smaller blood vessels with sudan III was observed. This local lipemia was often so intensive that it resembled the pictures seen in lipemic diabetes, and experimental hypercholesterinemia of herbivorous animals. The observation of identical characteristics in thyroid glands removed during life excludes the possibility of dealing with postmortem or degenerative changes.

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11. Martinez: Thyroid Insufficiency and Cholesterinemia, Trav. du. lab. de physiol. de la fac. de med. de Buenos Aires **16**:245, 1914.

12. Mellanby, E., and Mellanby, M.: The Experimental Production of Thyroid Hyperplasia in Dogs, J. Physiol. **55**:7, 1921.

13. Cameron and Carmichael: Contributions to the Biochemistry of Iodine: The Comparative Effects of Thyroid and Iodide Feeding on the Growth in White Rats and Rabbits, J. Biol. Chem. **45**:69, 1920.

14. Arton: Sulle modeficazioni del contenuto in lipoidi del fegato dopo tiroidectomia, Arch. di. sc. biol. **5**:22, 1923.

15. Abelin, Goldener und Kobori: Ueber die Bedeutung des Fettes fuer die Stoffwechselwirkung der Schilddruese, Biochem. Ztschr. **174**:232, 1926.

BIOMETRICAL STUDIES IN PATHOLOGY

V. THE RACIAL AND AGE INCIDENCE OF CANCER AND OF OTHER MALIGNANT TUMORS*

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AND
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BALTIMORE

In an earlier paper [1] we have discussed the general statistical characteristics of a group of persons on each of whom a necropsy had been performed at the Johns Hopkins Hospital. In the following discussion this particular group of persons will be designated as the *necropsied population* of the Johns Hopkins Hospital. This designation will conveniently and precisely distinguish the defined group of persons from, (*a*) the *total population* of the Johns Hopkins Hospital, by which is meant all persons who have been patients in that institution whether necropsied or not, and also from (*b*) the *general population,* which means all the persons belonging to some defined demographic or geographic unit, regardless of whether they were ever in a hospital or not—as for example the general population of Maryland. We have decided to undertake, as the first step in the detailed analysis of this collection of necropsy records, a thorough biometric study of the cases of malignant tumors of all sorts (carcinomas, sarcomas and other malignant tumors) which have occurred in this necropsied population. The present paper begins a series which will deal with this subject. It is proposed to discuss first the frequency of malignant tumors in this necropsied population with special reference to race, and to age. This will be followed in later papers by detailed discussion of such matters as location and type of tumors and relation to other lesions.

In the main such statistical information as exists on the cancer problem has been derived from the study of deaths recorded in official vital statistics as having been due to cancer. The results obtained in this way have never been entirely convincing, even within the limited field of discourse to which they are pertinent. There is a wide divergence of opinion among competent statisticians on even so theoretically simple a question as whether cancer is increasing or not. The reason for

* Papers from the Statistical Department of Johns Hopkins Hospital (no. 8) and from the Institute for Biological Research of the Johns Hopkins University.

1. Pearl, Raymond, and Bacon, Agnes L.: Biometrical Studies in Pathology: IV. Statistical Characteristics of a Population Composed of Necropsied Persons, Arch. Path. **1**:329-347 (March) 1926.

this condition is that official vital statistics about cancer mortality are, in detail, certainly unreliable. The diagnosis as to site of malignant growth in such official statistics is usually based solely on clinical evidence. There can be no comparison, on the score of accuracy, between such official statistics and those got from thorough and complete necropsies.

In the present state of knowledge regarding cancer it seems worth while to attempt to extract, and analyze biometrically, every bit of information which can be gleaned from the relatively large and thorough series of cancer necropsies which is available in our records. The results not only should be of interest to the pathologist, the surgeon and the clinician, but also perhaps suggestive to the experimental worker searching for the cause of cancer.

BASIC TABLE

In table 1 is tabulated every case of malignant tumor which occurred in the 6,670 persons comprising the necropsied population discussed in the earlier paper. Of these 6,670 persons, 816, or 12.2 per cent, showed some form of malignant tumor.

The material is first broken up into four groups on the basis of sex and color. These are white males, white females, colored males and colored females. No further racial division is attempted for the present. The material is next classified as to the kind of malignant tumor into the following groups:

I. Carcinomas and epitheliomas.

II. Sarcomas, and the other forms of malignant tumor not falling in class I.

In the second class are included, in addition to the different recognized and named varieties of sarcoma, all other types of malignant tumors not carcinomas, such as gliomas [2] of the brain, hypernephromas, malignant endotheliomas, malignant teratomas, etc. The details on this point are reserved for a later paper, in which the primary site and character of each tumor will be given. For the present discussion the foregoing broad classification is sufficient.

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2. The disposition of gliomas in a statistical tabulation of tumors is a knotty problem. As will be seen we have decided to call them as a class malignant. Ophüls (Stanford Univ. publ., M. Sc. **1**:319, 1926) divides his cases, between malignant and benign. This is unquestionably the logical thing to do, but the necropsy records here do not permit this division to be made with any certainty or accuracy. Cushing (Studies in Intracranial Physiology and Surgery, London, Oxford University Press, 1926) concludes from careful study of his cases that roughly about 60 per cent of gliomas are malignant and 40 per cent are benign.

RACIAL INCIDENCE OF MALIGNANT TUMORS

In table 2 are set forth the relative or percentage frequencies of occurrence of malignant tumors in the four sex-color portions of the necropsied population on which these studies are based. The absolute figures from which these percentages are derived will be found in table 1.

TABLE 1.—*Malignant Tumors, Classified by Sex, Color, Age and Kind of Tumor*

Sex and Color	Kind of Tumor	Age								No Record as to Age	Total
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	
Male											
White	I. Carcinomas and epitheliomas	..	1	7	23	65	85	81	28	3	1	294
	II. Sarcomas and other	11	10	18	25	22	22	10	1	..	1	120
	All malignant tumors	11	11	25	48	87	107	91	29	3	2	414
Colored	I. Carcinomas and epitheliomas	..	1	3	8	20	24	14	5	..	..	75
	II. Sarcomas and other	2	2	3	1	3	3	..	..	..	..	14
	All malignant tumors	2	3	6	9	23	27	14	5	..	..	89
Female											
White	I. Carcinomas and epitheliomas	..	2	3	20	52	40	34	7	..	1	174
	II. Sarcomas and other	10	5	11	11	12	7	3	..	..	1	60
	All malignant tumors	10	7	14	37	64	56	37	7	..	2	234
Colored	I. Carcinomas and epitheliomas	..	..	4	10	24	16	8	2	..	..	64
	II. Sarcomas and other	4	1	1	1	4	3	1	..	..	..	15
	All malignant tumors	4	1	5	11	28	19	9	2	..	..	79
Both Sexes All races	All malignant tumors	27	22	50	105	202	209	151	43	3	4	816

TABLE 2.—*The Relative Frequency of Occurrence of Malignant Tumors in the Necropsied Population of the Johns Hopkins Hospital*

Group	Total Numbers in Necropsied Population	Percentage of Total Necropsied Population Showing		
		I Carcinoma	II Sarcoma and Other Malignant Tumor	I and II Any Malignant Growth
White males	2,501	11.35	4.63	15.98
White females	1,320	13.18	4.55	17.73
All whites	3,911	11.97	4.60	16.57
Colored males	1,650	4.55	0.85	5.39
Colored females	1,109	5.77	1.35	7.12
All colored	2,759	5.04	1.05	6.09
All males	4,241	8.70	3.16	11.86
All females	2,429	9.80	3.09	12.89
Total	6,670	9.11	3.12	12.23

From table 2 the following facts emerge, concerning the necropsied population of the Johns Hopkins Hospital, over the period covered in the inquiry:

1. Some form of malignant tumor was found at autopsy in approximately 12.2 per cent of the 6,670 deaths. One in every 8.2 persons in this necropsied population had a malignant tumor at death.

2. Of the 6,670 persons 9.11 per cent had carcinoma and 3.12 per cent had sarcoma or some other malignant growth not carcinoma. This indicates, taking all classes together, that carcinoma was relatively much more frequent than malignant tumors not carcinoma. Obviously this relationship may be greatly disturbed if a given hospital is for any reason attracting into its population a particular type of cancerous person, and is getting an undue proportion of necropsies of such persons. Just this thing occurs to some extent in the present statistics, in the case of gliomas of the brain. These tumors are represented in this material in probably unduly high frequency, as compared with what a random sample of a general population would show, because of the special development of brain surgery in this hospital.

3. Of the 816 cases of malignant new growth shown in table 1, 607 were carcinomatous, and 209, or 25.61 per cent, were sarcomas and other malignant tumors not carcinomatous. Whipham [3] found, in 650 carefully studied cases of malignancy, 154, or just under 23 per cent, noncarcinomatous malignant tumors (sarcoma and endothelioma). The substantial agreement of this entirely independent set of observations with the Johns Hopkins Hospital experience on this point is interesting. Ophüls [2] found 115 sarcomatous (and other) tumors in a total of 512 malignant cases, or 22.46 per cent. This figure again agrees well with the other experiences cited. In general it seems reasonable to conclude that of every four or five persons having a malignant tumor, if they are chosen at random from among all such persons, one will have sarcoma or some other noncarcinomatous form of malignancy, while the others will have a carcinoma or epithelioma.

4. Malignant tumors of all kinds taken in the aggregate tend to occur a little more frequently, relatively, among females than they do in males in this necropsied population. This is true of both colored and white racial groups. This tendency is, however, small in magnitude, and disappears entirely in the sarcoma group where the percentage for all males is slightly (but insignificantly) higher than that for all females.

The relative frequencies of table 2 may first be compared with corresponding percentages for certain general populations in table 3 and chart 1. All persons in a necropsied population are dead, in the nature of the case. Therefore, the figures in table 2 are the percentages of deaths of persons having malignant tumors out of all deaths, in a particular defined population. Similar figures will be obtained for a general population if the percentage of deaths from cancer and other malignant tumors to all deaths, from whatever cause, is calculated for that population. Actually the comparison is quite justifiable, because

3. Whipham, T. R. C.: J. Path. & Bact. **12**:322-353, 1908.

according to the rules by which official vital statistics are recorded, if a person is known to have cancer the death must be recorded as primarily due to that, even though pneumonia or some other disease may actually have been the terminal cause of the demise.[4] In table 3 are given the percentages of deaths from "cancer and other malignant tumors" (rubrics 43-49 inclusive, of the International Classification) to deaths from all causes, in three general populations, with as great specificity as can be obtained from the official records[5] for the year 1922. The data for the Registration Area are taken from tables *7A* and *7B;* those for Maryland from table 8, and those for Baltimore from table 9 of the report referred to.

From table 3 and chart 1, taken in comparison with table 2, it appears that malignant tumors occur in a larger proportion of the deaths of a necropsied population than they do in corresponding sex-color groups of the general population. This is in spite of the fact that persons in the

TABLE 3.—*The Relative Frequency of Deaths from Cancer and Other Malignant Tumors in Certain General Populations—1922*

	Registration Area			Maryland			Baltimore		
Group	Total Deaths	Cancer, etc., Deaths	Per Cent	Total Deaths	Cancer, etc., Deaths	Per Cent	Total Deaths	Cancer, etc., Deaths	Per Cent
White males	507,567	33,275	6.56	15,453	1,296	8.39	8,423	798	9.47
White females	443,885	42,306	9.53						
Colored males	68,360	1,388	2.03	4,813	186	3.86	2,401	112	4.66
Colored females	64,140	2,909	4.54						
Total	1,083,952	79,877	7.39	20,266	1,482	7.31	10,824	910	8.41

cancer age periods are generally under-represented in the necropsied population, as was shown in the preceding paper in this series.[1] The explanation of this difference probably lies mainly in the fact that cancer is, in a peculiar degree, a disease for which treatment in a hospital offers the only possible hope of relief. It is therefore to be expected that cancerous persons will tend to be relatively in excess, both in hospital populations, and in necropsied populations, as compared with the general population.

In the Registration Area as a whole the percentage of deaths from cancer to all deaths is approximately three times as great in white males as it is in colored males, and approximately twice as great in white females as in colored females. These ratios are in the same sense and of about the same magnitude as those shown in table 2 for the autopsied material. The experience of the Industrial Department of the Metro-

4. Pearl, Raymond: Introduction to Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923.

5. Mortality Statistics, 1922, Washington (Bureau of the Census), 1925.

politan Life Insurance Company [6] shows a male white death rate 1.5 times the male colored death rate, from all forms of cancer taken together. But the cancer death rate in colored females in this insurance experience is actually higher, by an amount probably insignificant statistically, than in white females. It must be remembered, however, that the comparisons up to this point have been of death *ratios* and not, except in the case of the Metropolitan Life Insurance Company experience, of death *rates*. And on the point at issue these two expressions may give quite different results. The following example will make this plain. In Washington, D. C., in 1921, the "refined" death rate for

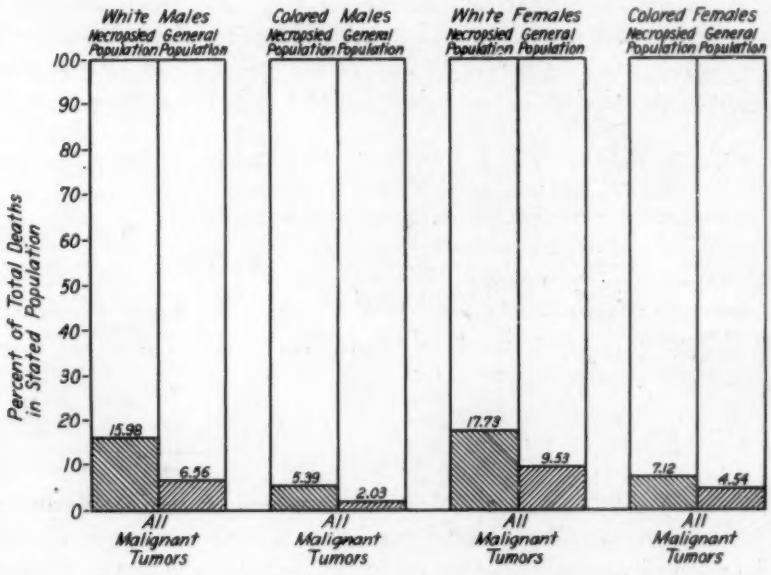

Chart 1.—The relative proportion of deaths from malignant tumors to all deaths, in the necropsied population of the Johns Hopkins Hospital, and the general population of the Registration States in 1922.

cancer and other malignant tumors was 100.7 for whites and 100.3 for colored.[7] But in 1922, 9.8 per cent of the total deaths among whites in Washington were due to cancer and other malignant tumors, while but 4.7 per cent of the total deaths among the colored were due to the causes in this category.

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6. Dublin, L. I.; Kopf, E. W., and Van Buren, G. H.: Cancer Mortality Among Insured Wage-Earners and their Families, Metropolitan Life Insurance Company, 1925, p. 24.

7. Mortality Statistics, 1922, p. 49. "Refined" denotes a death rate, corrected for age, and for nonresident deaths.

The question of the relative frequency of cancer in the colored race, as compared with the white races, is of sufficient theoretical importance to warrant careful analysis. Both death rates and death ratios may be misleading in this connection, when they are taken for the population as a whole, including all ages. Age specific death rates and ratios are needed. In the age periods in which cancer is an important cause of death one of these expressions of mortality is quite as accurate and reliable as the other, provided each is made specific for a range of age not too great in extent. But they describe, of course, different aspects of mortality.

The experience of the Metropolitan Life Insurance Company may be first considered. Table 4 is condensed from table 7 of Dublin, Kopf, and Van Buren.[6]

In each group in table 4 the white male rates are higher than the colored male rates. The same is true of the females after the age 45.

TABLE 4.—*Death Rates, per 100,000 Persons Exposed, from all Forms of Cancer by Color, Sex and Age—Experience of Metropolitan Life Insurance Company Industrial Department*

	White		Colored	
Age Period	Male	Female	Male	Female
1–24	2.7	2.6	2.1	3.2
25–34	8.9	19.8	7.9	32.5
35–44	38.6	96.4	30.4	118.4
45–54	147.0	235.1	85.7	230.0
55–64	375.6	422.5	194.4	306.1
65–74	666.8	685.1	286.3	484.8
75 and over	905.7	920.5	450.7	564.4

Prior to that age the rates for colored females are higher than those for the white females. The thought comes at once to mind that this reversal of the racial relations, in females aged less than 45, is in some manner associated with differences in sexual and reproductive activity in the females of the two races, and perhaps such connected matters as relative incidence of venereal diseases. But before proceeding too far along this line of thought it will be well to examine other data, because the Metropolitan Life Insurance Company's colored industrial policy holders are perhaps not an entirely representative sample of the colored population in general.

Unfortunately it is impossible to get entirely satisfactory data for the general population of any large part of the United States, from which exact comparisons may be made between the colored and white cancer death rates. For those parts of the country where the negro population is largest, relative to the white, either vital statistics are lacking entirely, or the quality of death registration does not inspire confidence in the completeness or reliability of the published figures.

Taking all elements of the case into consideration, it is our opinion that the most reliable official American data existing at present on which to base a critical comparison of cancer death rates in the colored and white races are those for Baltimore and New York City. The registration of deaths in both these cities is as complete and accurate as it is humanly possible to obtain in this country at this time. It compares

TABLE 5.—*Age Specific Death Rates per 100,000 Population, for Cancer and Other Malignant Tumors, by Sex and Color (Rates for Deaths Numbering Less Than Five Are Shown in Bold Face)*

Place, Year and Group	Under 5	5-9	10-14	15-19	20-24	25-34	35-44	45-54	55-64	65-74	75 and Over
Baltimore, 1910											
White males	**4.4**	**4.6**	**4.8**	**4.5**	..	12.6	68.7	185.1	402.3	496.7	704.5
Colored males	..	..	..	..	..	**11.7**	**14.6**	**67.4**	269.1	**386.7**	....
Difference	+4.4	+4.6	+4.8	+4.5	..	+0.9	+54.1	+117.7	+133.2	+130.0	+704.5
White females	..	**9.3**	..	..	..	23.9	99.9	299.9	560.0	753.0	839.4
Colored females	..	..	..	**22.1**	**17.1**	**10.2**	104.1	284.2	434.4	**297.8**	**243.3**
Difference	..	+9.3	..	−22.1	−17.1	+13.7	−94.2	+15.7	+125.6	+455.1	+596.1
Baltimore, 1920											
White males	**6.5**	**3.5**	..	..	**6.8**	21.5	68.2	204.0	430.4	969.9	1054.6
Colored males	..	..	..	..	**17.0**	**34.6**	**30.1**	161.8	382.6	501.0	**753.7**
Difference	+6.5	+3.5	..	..	−10.2	−13.1	+38.1	+42.2	+47.8	+468.9	+260.9
White females	**3.3**	..	..	18.1	**3.3**	28.7	116.7	224.1	483.2	747.5	931.1
Colored females	**23.2**	..	..	..	..	49.7	159.3	395.0	578.0	508.8	**211.4**
Difference	−19.9	..	..	+18.1	+3.3	−21.0	−42.6	−170.9	−94.8	+243.7	+719.7
New York City, 1910											
White males	7.1	**0.9**	1.4	4.2	10.2	12.8	44.9	175.7	402.8	745.4	694.2
Colored males	..	..	..	..	..	..	**39.5**	107.9	325.3	**187.6**	....
Difference	+7.1	+0.9	+1.4	+4.2	+10.2	+12.8	+5.4	+67.8	+77.5	+557.8	+694.2
White females	2.8	2.3	1.4	3.4	2.6	25.8	106.2	281.6	502.4	671.2	894.4
Colored females	..	..	..	..	**13.7**	47.4	201.1	367.1	421.7	**537.6**	**649.4**
Difference	+2.8	+2.3	+1.4	+3.4	−11.1	−21.6	−94.9	−85.5	+80.7	+133.6	+245.0
New York City, 1920											
White males	3.6	1.1	1.2	4.2	5.0	14.2	50.8	189.2	523.2	851.5	1008.6
Colored males	..	..	..	..	**10.9**	**18.2**	56.3	160.4	236.5	**400.0**	**450.5**
Difference	+3.6	+1.1	+1.2	+4.2	−5.9	−4.0	−5.5	+28.8	+286.7	+451.5	+558.1
White females	5.5	2.3	1.7	2.6	5.6	17.2	103.8	235.8	529.6	810.4	996.0
Colored females	..	..	..	..	..	35.5	134.3	187.4	613.0	455.8	**480.8**
Difference	+5.5	+2.3	+1.7	+2.6	+5.6	−18.3	−30.5	+48.4	−83.4	+354.6	+515.2

favorably in these respects with the death registration in any city in the world. In both cities the colored population is absolutely large. In Baltimore there were 85,095 colored persons in 1910, and 108,696 in 1920. The corresponding figures for New York City were 97,721 and 160,585.

We shall next present the age specific death rates for colored and whites, derived from the mortality experience of these two cities, Baltimore and New York City. The figures of our table 5 are extracted

from table IV of the comprehensive and useful report of the Bureau of the Census on mortality rates.[8] In table 5 a difference is marked + (plus) when the rate for the whites is *higher* than that for the colored, and — (minus) when the white rate is *lower* than the colored.

In order to bring out clearly the nature of the differences, and also to show the form of the cancer specific death rate curves, charts 2

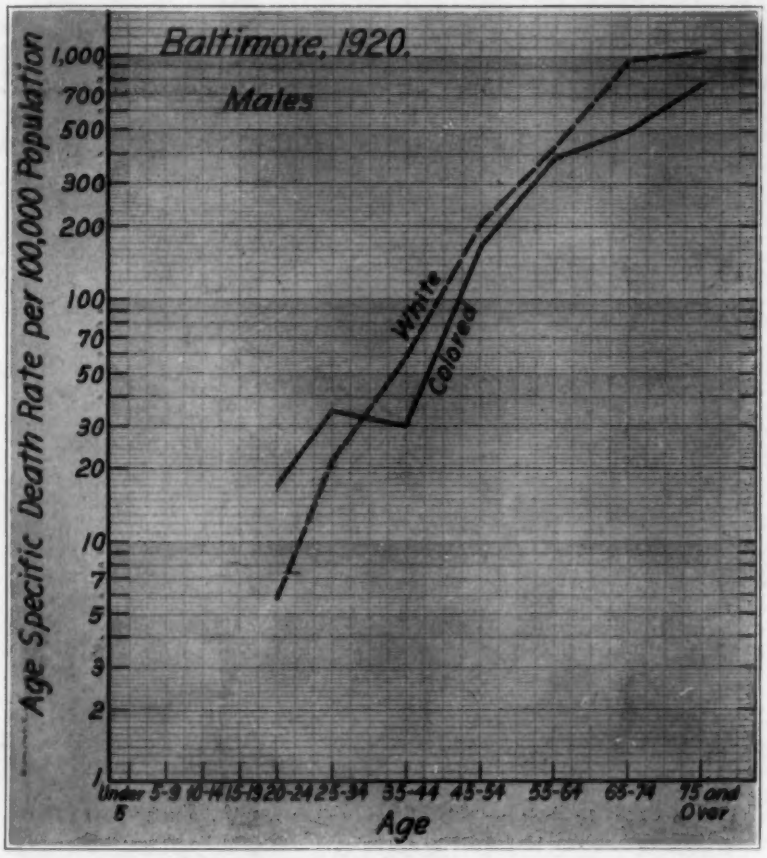

Chart 2.—Age specific death rates from cancer and other malignant tumors in white and colored males in Baltimore, 1920.

to 5 are presented. These give, for the year 1920, the age specific death rates in the white and colored in the two cities, Baltimore and New York.

From table 5 and charts 2 to 5 it is seen that:

1. In 1910, in both Baltimore and New York City, the death rates of white males from malignant growths of all sorts were higher at

8. Mortality Rates 1910-1920, Washington, Bureau of the Census, 1923.

all ages than were the corresponding rates for colored males. This is in agreement with the Metropolitan Life Insurance Company's experience cited previously.

2. The same relationship between the cancer deaths of the males of the two racial groups held in 1920 in these two cities, except that in the age groups between 20 and 34, in the case of Baltimore, and between

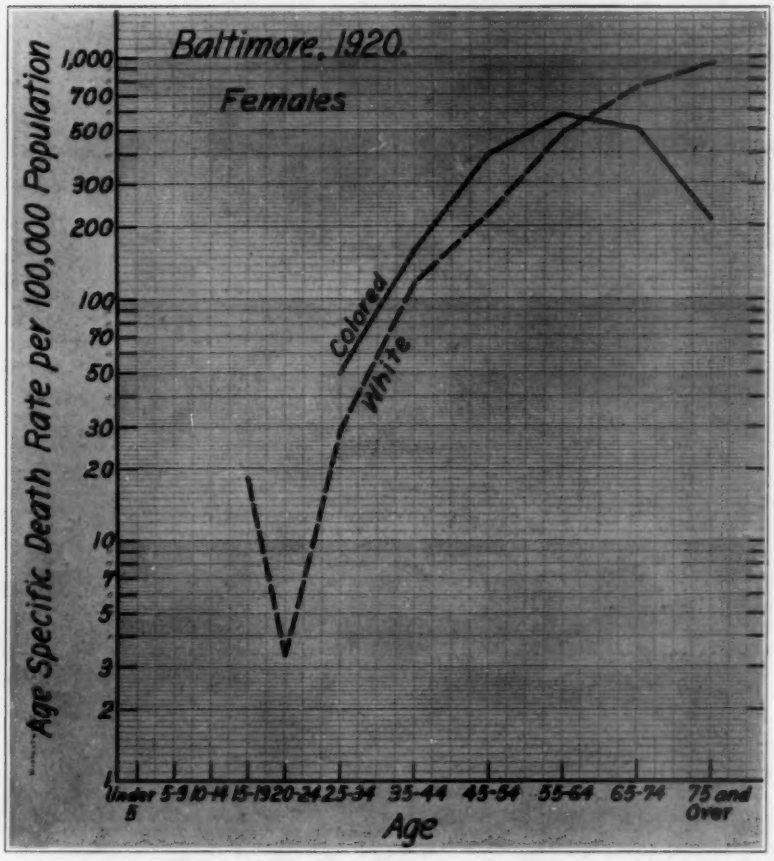

Chart 3.—Age specific death rates from cancer and other malignant tumors in white and colored females in Baltimore, 1920.

20 and 44, in the case of New York City, the rates were higher for the colored than the white. These differences are not large, however, and it is entirely possible that they represent merely fluctuations of sampling, without real biologic significance.

3. In the females there is a definite tendency for the cancer death rates of the colored to be higher than those of the whites, during the child bearing period of life, and perhaps during the following decade.

This result again is in general agreement with the Metropolitan Life Insurance Company's experience. It seems to us probable that this excess is an expression of a real biologic differentiation.

There is another bit of evidence to be obtained from official death rates on this question of race incidence. On page 86 of "Mortality Rates 1910-1920" [8] are given the adjusted death rates from cancer and

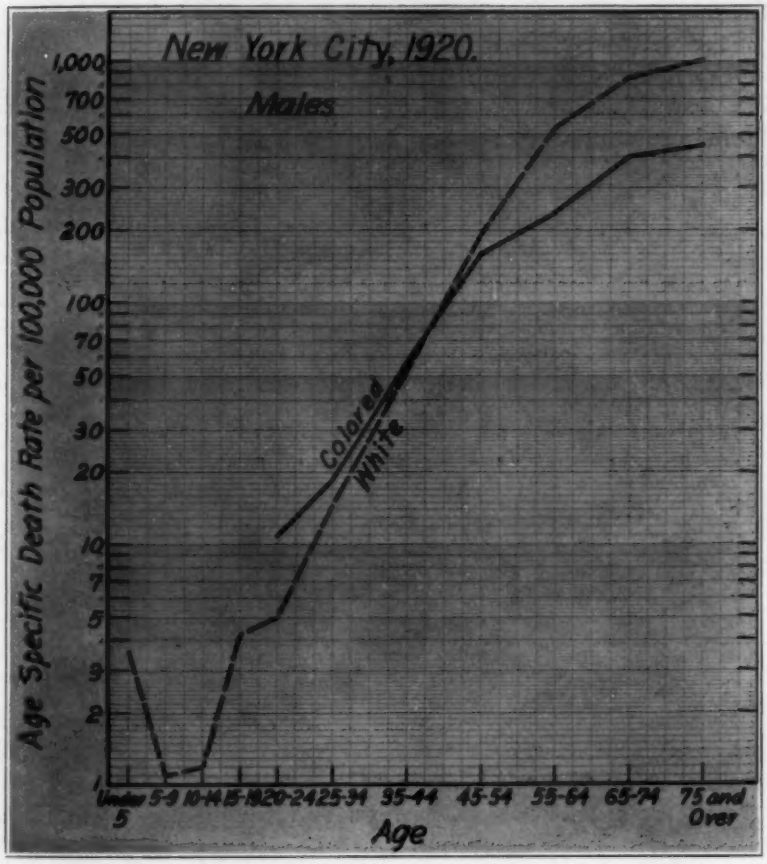

Chart 4.—Age specific death rates from cancer and other malignant tumors in white and colored males in New York City, 1920.

other malignant tumors in some fourteen cities and states containing a sufficiently large colored population to warrant separate treatment. The death rates are adjusted for age on the basis of the Registrar-General's standard million of population. From this material we have put together table 6.

From table 6 it appears that in every city and state listed, except one (Mississippi), the death rate from cancer and other malignant growths

was higher in the white population than in the colored, after correcting for the age distributions of the exposed. This table brings out in a striking manner another point, which incidentally indicates that no weight is to be attached to the single apparent exception to the general rule regarding racial incidence. No vital statistician informed as to the real facts will question the assertion that the registration of deaths is by a considerable degree more complete and more accurate in the cities and states listed in the upper (*A*) portion of the table, than it is in the states listed in the lower (*B*) portion. Now the table itself shows that the *lowest* adjusted cancer rates in the upper (*A*) half of table 6 are 82.4 for whites, and 76.5 for colored. But the *highest* adjusted cancer rates in the lower (*B*) half of the table are 65.1 for whites, and 61 for colored. This relatively enormous gap between the

TABLE 6.—*Adjusted Death Rates from Cancer and Other Malignant Tumors per 100,000 Population*

	White	Colored	Difference
A. Cities and states in which the registration of deaths has a relatively high order of reliability and completeness			
Baltimore	105.5	97.9	+ 7.6
New York City	105.2	78.9	+26.3
Chicago	104.6	96.7	+ 7.9
New York State	92.4	78.2	+14.2
Maryland	88.2	76.5	+11.7
Pennsylvania	82.4	82.1	+ 0.3
B. States in which the reliability and completeness of the registration of deaths are less certain			
Louisiana	65.1	57.8	+ 7.3
Virginia	61.6	61.0	+ 0.6
Florida	58.2	50.2	+ 8.0
Kentucky	57.7	56.9	+ 0.8
Tennessee	52.3	47.1	+ 5.2
South Carolina	51.9	38.4	+13.5
North Carolina	51.0	44.6	+ 6.4
Mississippi	47.6	48.3	— 0.7

lowest cancer rates in localities with accurate and comprehensive death registration, and the highest cancer rates in localities with distinctly less effective registration, cannot conceivably be regarded, in our judgment, as an expression of a real biologic difference in the incidence of cancer in the northern and southern portions of the United States. On the contrary, we believe it to be manifestly nothing more than a reflection of the inadequacy of death registration in the South, particularly as concerns causes of death. Or, to put the case in another way, it is *possible* that cancer occurs and kills less frequently in the South than it does in the North, having regard to the ages and racial distributions of the population exposed to risk. But existing mortality statistics furnish no conclusive evidence that this is the case. The *prima facie* indications of these existing vital statistics are plainly misleading on the point, and probably highly so.

Let us turn now to one further and final body of evidence regarding the relative incidence of cancer and other malignant tumors in the

white and colored races. In table 7 are given, for the Registration States in 1922, the age specific *death ratios* for cancer and other malignant tumors, by color and sex. These ratios were computed from data given in tables 7 *A* and 7 *B* of *Mortality Statistics 1922,* the official publication of the Bureau of the Census. The total absolute number of deaths, on which the ratios of table 7 are based, are as follows:

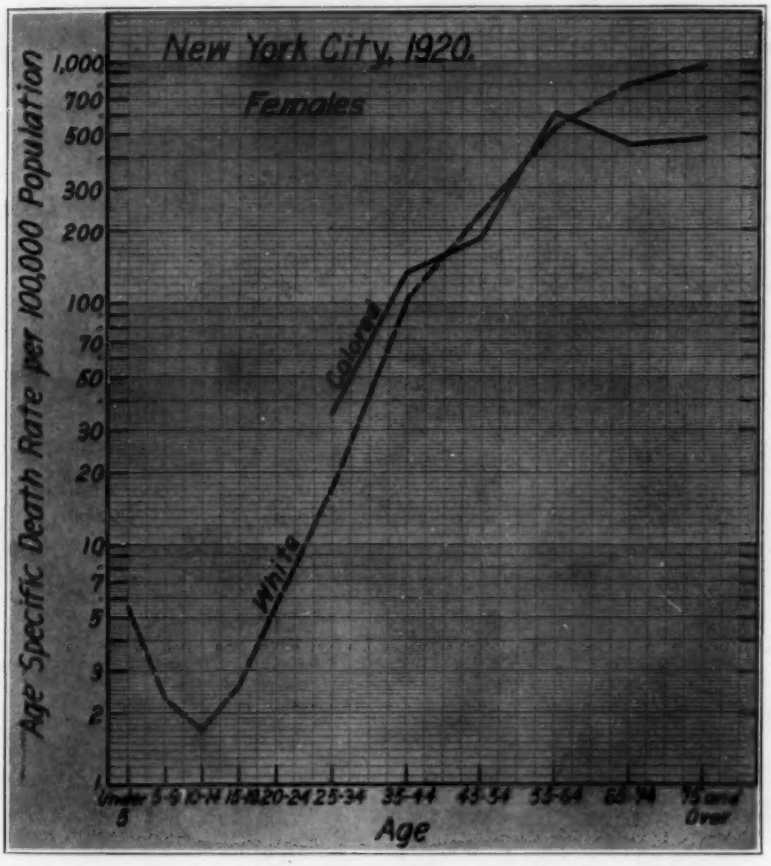

Chart 5.—Age specific death rates from cancer and other malignant tumors in white and colored females in New York City, 1920.

White males	506,945 [9]
White females	443,539
Colored males	67,995
Colored females	63,834

9. This and the following figures differ from the total deaths in the Registration States in 1922, by the number of deaths of persons of unknown age in each group.

The death ratios of table 7 are the *percentages* of the deaths attributed to cancer and other malignant tumors to the deaths from all causes, within each age group. Thus, for example, in the age group 25-29 there were 14,448 deaths of white males from all causes in 1922. Of these 14,448 deaths 229 were attributed to cancer and other malignant tumors in the official vital statistics. Therefore we have:

White males, age 25-29; death ratio $= \frac{229 \times 100}{14,448} = 1.585$.

This is the value tabulated in the white male column against the age argument 25-29.

TABLE 7.—*Death Ratios (Percentage of Cancer Deaths to all Deaths) by Sex, Age and Color—Registration States, 1922*

Age	White Males. Cancer Death Ratio, per Cent	White Females. Cancer Death Ratio, per Cent	Colored Males. Cancer Death Ratio, per Cent	Colored Females. Cancer Death Ratio, per Cent
Under 5	0.153 ± 0.008	0.153 ± 0.009	0.042 ± 0.011	0.065 ± 0.015
5- 9	0.688 ± 0.053	0.708 ± 0.059	0.504 ± 0.128	0.227 ± 0.088
10-14	0.902 ± 0.048	1.219 ± 0.093	0.538 ± 0.137	0.581 ± 0.138
15-19	1.366 ± 0.076	0.911 ± 0.065	0.321 ± 0.076	0.395 ± 0.074
20-24	1.294 ± 0.068	1.253 ± 0.064	0.443 ± 0.070	0.741 ± 0.085
25-29	1.585 ± 0.070	2.645 ± 0.088	0.676 ± 0.089	2.171 ± 0.150
30-34	2.392 ± 0.081	5.779 ± 0.127	1.310 ± 0.134	4.188 ± 0.225
35-39	3.653 ± 0.090	9.860 ± 0.155	1.446 ± 0.126	5.836 ± 0.247
40-44	5.840 ± 0.109	16.272 ± 0.191	2.846 ± 0.174	9.627 ± 0.319
45-49	8.195 ± 0.118	19.865 ± 0.172	3.832 ± 0.197	11.327 ± 0.349
50-54	10.900 ± 0.124	21.202 ± 0.184	3.876 ± 0.193	9.677 ± 0.331
55-59	12.709 ± 0.126	21.014 ± 0.175	4.962 ± 0.256	10.129 ± 0.380
60-64	12.917 ± 0.114	17.650 ± 0.144	5.561 ± 0.273	10.653 ± 0.378
65-69	12.501 ± 0.109	15.369 ± 0.130	5.142 ± 0.272	8.864 ± 0.336
70-74	11.301 ± 0.104	12.310 ± 0.114	4.361 ± 0.255	7.217 ± 0.355
75-79	8.891 ± 0.100	9.338 ± 0.103	3.253 ± 0.258	4.589 ± 0.341
80-84	6.482 ± 0.104	6.954 ± 0.102	1.864 ± 0.224	4.099 ± 0.341
85-89	4.988 ± 0.130	5.534 ± 0.120	1.720 ± 0.297	2.965 ± 0.389
90-94	3.357 ± 0.191	4.076 ± 0.176	1.242 ± 0.340	2.147 ± 0.383
95-99	2.247 ± 0.353	2.975 ± 0.317	0.488 ± 0.328	0.851 ± 0.404
100 and over	3.049 ± 0.906	1.167 ± 0.452	0	2.869 ± 0.721

The data of table 7 are shown graphically in chart 6.

From table 7 and chart 6 it clearly appears that at all ages from 25 on the cancer death ratios are higher in the whites than in the corresponding group of the colored. Cancer is a relatively much more frequent (or important) cause of death in the whites than in the colored. The amount of the excess is large, especially in the ages from 40 to 80.

These data also bring out a number of interesting points about the age incidence of cancer relative to sex and race, but discussion of these points will be deferred to the next section of this paper.

Taking all the data together it can be regarded as established, we believe, that in general malignant new growths occur with considerably greater frequency in the white race than in the colored, in the United States. All lines of evidence concur in support of this conclusion—necropsy records, age corrected death rates for general population, and death ratios specific for age and sex. The only apparently significant

exception to this general conclusion is found in the fact that, during the child-bearing ages, colored females exhibit a higher incidence of malignancy than do the white females. The generally less frequent occurrence of malignant neoplasms in the negro may indicate a lower susceptibility of truly genetic, racial origin, reflecting a real biologic differentiation of colored from white, in this respect. But one should be cautious about drawing such a conclusion on the basis solely of the evidence so far presented. All that we have shown is that cancer and other malignant tumors do occur more frequently among whites than among negroes, with the exception noted. The data which have been

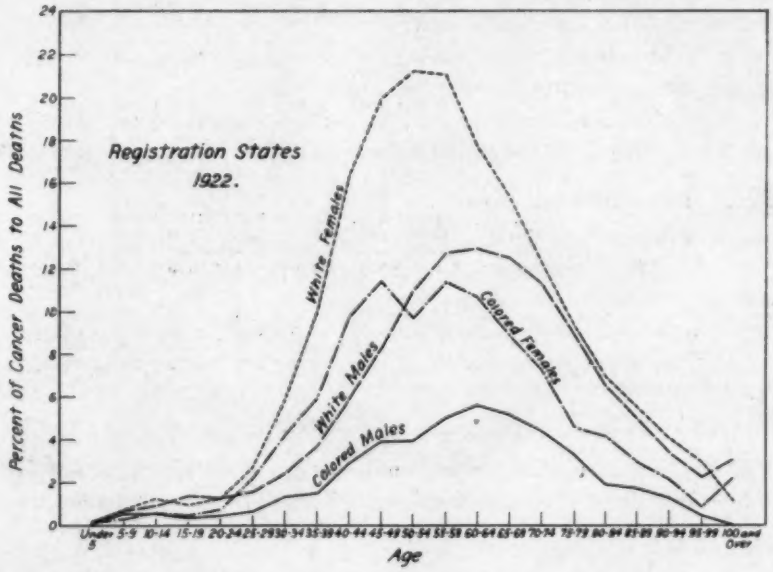

Chart 6.—Cancer death ratios by color, sex and age; solid line indicates colored males; dash line, white males; dash-dot line, colored females; dot line, white females.

presented give virtually no evidence as to why this is so. It *probably* is because of innate biologic differentiations embodied in the two races. But, on the other hand, the environment of the whites is, in many respects, different from that of the colored. It is possible that these differences in the biologic and physical environment play a significant part in determining the observed differences in cancer incidence in these two broad racial groups. The main point to be kept in mind for the present is that the evidence so far reviewed permits no final conclusion on the point as to whether the greater susceptibility of the whites than of the colored to cancer finds its origin in inherited racial differences, or in purely environmental differences.

AGE INCIDENCE OF MALIGNANT TUMORS

In table 1 are given the raw frequencies of the cancer incidence by age in the necropsied population of the Johns Hopkins Hospital. The biometric constants derived from these distributions are shown in table 8.

TABLE 8.—*Biometric Constants for Age of Persons in the Necropsied Population Having Cancer or Other Malignant Tumor*

Sex and Color	Kind of Tumor	Mean Age, Years	Median Age, Years	Standard Deviation, Years	Coefficient of Variation, per Cent
Male White	I. Carcinomas and epitheliomas	55.59 ± 0.48	55.94 ± 0.60	12.11 ± 0.34	21.8 ± 0.6
	II. Sarcomas and other	37.37 ± 1.11	38.20 ± 1.39	17.93 ± 0.79	48.1 ± 2.5
	All malignant tumors	50.33 ± 0.54	52.24 ± 0.67	16.29 ± 0.38	32.4 ± 0.8
Colored	I. Carcinomas and epitheliomas	51.94 ± 0.96	52.29 ± 1.20	12.35 ± 0.68	23.8 ± 1.4
	II. Sarcomas and other	31.91 ± 3.27	30.00 ± 4.09	18.11 ± 2.31	56.8 ± 9.3
	All malignant tumors	48.79 ± 1.00	50.56 ± 1.36	15.28 ± 0.77	31.3 ± 1.7
Female White	I. Carcinomas and epitheliomas	51.04 ± 0.60	50.71 ± 0.75	11.61 ± 0.42	22.7 ± 0.9
	II. Sarcomas and other	31.93 ± 1.61	33.18 ± 2.01	18.39 ± 1.14	57.6 ± 4.6
	All malignant tumors	46.18 ± 0.71	47.50 ± 0.89	15.99 ± 0.50	34.6 ± 1.2
Colored	I. Carcinomas and epitheliomas	48.37 ± 0.95	47.50 ± 1.19	11.26 ± 0.67	23.3 ± 1.5
	II. Sarcomas and other	32.98 ± 3.85	41.25 ± 4.81	22.10 ± 2.72	67.0 ± 11.4
	All malignant tumors	45.44 ± 1.16	46.61 ± 1.45	15.23 ± 0.82	33.5 ± 2.0

From table 8 the following points are to be noted.

1. In cases of carcinomatous tumors the age distributions are fairly symmetrical about their mean values. The differences between means and medians for this group of tumors are as follows:

Carcinomas

White males ..... mean—median = —0.35 ± 0.77
Colored males ..... mean—median = —0.35 ± 1.54
White females ..... mean—median = +0.33 ± 0.96
Colored females ..... mean—median = +0.87 ± 1.52

Obviously none of these differences is significant.

The case is much the same in the sarcoma group, though the absolute differences are larger. There the following differences are found:

Sarcomas and other

White males ..... mean—median = —0.83 ± 1.78
Colored males..... mean—median = +1.91 ± 4.24
White females ..... mean—median = —1.25 ± 2.58
Colored females..... mean—median = —8.27 ± 6.16

2. The present material indicates that persons having carcinoma die at a much higher average age than those having sarcoma. Half of the male white persons in this experience who died with carcinoma survived to an average age of 55.94 years of age before death, whereas a half of the white males who died of sarcoma did so before age 38.2 years. Similar differences appear in all the other sex-color groups. The mean age at death of all our white male carcinoma patients was 55.59 ± 0.48 years. Lazarus-Barlow [10] found the mean age at death of 2,073 male carcinomatous patients at the Middlesex Hospital to be 55.2 years. Closer agreement than this could not reasonably be expected. In 4,659 cases of carcinoma in females he found the mean age at death to be 49.9 years, which is not in quite so good agreement with our figure of 51.04 ± 0.60 years, but the difference is not statistically significant.

3. The colored persons in this necropsied population who die with malignant tumors, tend to do so at an earlier age, on the average, than do whites. The only exception is in the case of the female sarcomatous groups.

TABLE 9.—*Biometric Constants for Age of Persons in the General Population of the Registration States in 1923, Dying of Cancer or Other Malignant Tumors*

Sex	Color	Mean Age, Years	Median Age, Years	Standard Deviation, Years	Coefficient of Variation, per Cent
Male	White	62.604 ± 0.050	64.244 ± 0.063	14.139 ± 0.036	22.573 ± 0.060
	Colored	56.246 ± 0.276	56.483 ± 0.345	15.710 ± 0.195	27.931 ± 0.373
Female	White	60.411 ± 0.046	61.382 ± 0.058	14.488 ± 0.033	23.982 ± 0.057
	Colored	52.401 ± 0.186	51.511 ± 0.233	15.371 ± 0.132	29.333 ± 0.272

4. Cancerous females, so far as may be judged from this necropsied population, tend to die at an earlier age, on the average, than do cancerous males. This is true of both carcinoma and sarcoma in the whites, and of carcinoma in the colored. The reverse relation appears in the colored sarcoma group, but the numbers involved there are too small to be significant.

5. There is a rather high degree of variation in the ages at death from malignant tumors. This is manifested both by the standard deviations and by the coefficients of variation. This variability is more marked in the case of sarcoma than it is in carcinoma.

Let us now compare the biometric constants for the age distribution of malignant tumors in the necropsied population with the corresponding constants for the general population, with as much specificity as the official vital statistics permit. Table 9 gives the same constants as those

10. Lazarus-Barlow, W. S.: Arch. Middlesex Hosp. **5**: 26-46, 1905.

of table 8 for the distribution of persons recorded as dying of cancer and other malignant tumors in the Registration States in 1923.[11]

The immediate and striking result which emerges from a comparison of table 9 with table 8 is that the mean and median ages at death from cancer and other malignant tumors are much higher in the general population than they are in the necropsied population. There are probably several reasons for this uniform and substantial difference. The first of these, and probably the most important, is the one discussed in the preceding paper in this series,[1] that a necropsied hospital population has in general a different age distribution than does a general population. The necropsied population as a whole has an under-representation of aged persons, and an over-representation of young and middle-aged adults. The cancerous sample drawn out of the whole necropsied population seems to have these same characteristics. In the second place there is probably a systematic error relative to age in the vital statistics of the general population in respect of the diagnosis of malignancy. It seems probable that the cases of a considerable number of persons under 30 years of age in the present material, who were shown by autopsy to have died with a malignant tumor, would not have been so diagnosed and reported in the official vital statistics, if they had died outside the hospital and had not been subjected to necropsy. Probably many cases of death of young persons from lymphosarcoma are not recognized as such by general practitioners who make out death certificates.

It is interesting to note, however, that table 9 shows the same relations between colored and white, and between the sexes, in respect of mean age at death, that were found for the necropsied population in table 8. It seems fairly established that males die from cancer and other malignant tumors at a higher average age than do females, and that whites have a higher average age at death from these causes than do colored persons.

In a study of the official mortality statistics of Baltimore, regarding deaths from cancer of all forms, made some years ago by C. Hampson Jones,[12] the following mean ages at death were found:

White persons	57.689 years
Colored persons	49.454 years

It will be noted that these figures are intermediate between those of table 8 and table 9.

Turning back for a moment to table 7 and chart 6 we see that the ages at which cancer and other malignant tumors are relatively more

11. Data from Mortality Statistics, 1923, Washington, Bureau of the Census, 1925.

12. Jones, C. H.: Maryland M. J. **48**:337-343, 1905.

important causes of death than they are at any other ages show the same relationship so far as concerns the sexes. In white males cancer reaches its maximum importance as a lethal agent (that is, causes the largest proportions of all deaths) in the age period 60-64, whereas the corresponding age period for white females is ten years earlier (50-54). In colored males the peak death ratio is in the age period 60-64, while in females it occurs in the quinquennium 45-49. But the highest portion of the female colored death ratio curve is irregular, presumably because of fluctuations due to sampling, and it cannot safely be asserted that there is any real difference between the colored and the white races in the age at which cancer causes the highest proportion of all deaths.

Table 7 and chart 6 bring out in a striking manner the fact that at all ages cancer and other malignant tumors are relatively much less important causes of death in the colored race than they are in the corresponding moieties of the white race. Other lethal agents leave much less work for cancer to do among the negroes.

Before leaving the discussion of age distribution it is to be noted that in the 816 malignant cases, table 1 shows that there were three of carcinoma in persons under 20 years of age. Since carcinoma occurs only rarely at such early ages further details are given here about these three cases.

190. White female, aged 18, April 19, 1891. Very large, solid, and partly cystic tumor of left ovary, of which microscopic study was made, leading to the conclusion that it "appeared to be adeno-carcinoma." Pulmonary edema and atelectasis; fatty liver; fatty degeneration of kidney; secondary tumors in liver and lymphatic glands; edema of lower extremities.

It will be noted that this is an early necropsy in the series, and there seems to be the possibility of reasonable doubt that the tumor was a carcinoma. Since, however, there is no way of telling now what it really was, the original record is taken at its face value. About the two following cases there can be no doubt.

6111. White female, aged 17, Jan. 7, 1920. Adenocarcinoma of rectum, with metastases to regional lymph glands; operation for removal of diagnostic specimen; acute diffuse peritonitis; bronchopneumonia and fibrinous pleurisy.

7223. White male, aged 17. Nov. 10, 1922. Epidermoid carcinoma of hypophysial duct invading third ventricle and compressing sella and hypophysis. Hydrocephalus, involving especially the fifth ventricle. Feminine distribution of fat. Infantile genitalia. Lymphoid hyperplasia ileum. Recent operation for brain tumor. Section of right optic nerve and tract. Partial removal of tumor. Acute meningitis. Thrombus sinus rectus. Focal necroses in liver. Obsolete tubercle (?) in spleen.

DEATH RATES IN THE NECROPSIED POPULATION

The most comprehensive, accurate and instructive way of exhibiting the age incidence of mortality is in the form of life table death rates. Such figures show the number of deaths per thousand person-years

exposed to risk of dying, at the specified ages. Tables 10 to 13, inclusive, give such data for the necropsied population of Johns Hopkins Hospital, and for various parts of that population. The function tabulated here is the simple, ungraduated and unsmoothed central death rate m_x, got by dividing the absolute number of deaths in the age group by the person-years (life-years) exposure to risk in that group. These are the basic data of a life table. If any reader wishes to go on to the calculation of the other constants, q_{xx} and, d_x, $l\,\mathring{e}_x$ these data will enable him to do so, though in our judgment the special nature of the material, as well as its meagerness, do not warrant such refined computation.

From tables 10 to 13 a number of points of interest emerge. In the first place it is to be noted that the total experience presented by this

TABLE 10.—*Death Rates for Male Whites in the Necropsied Population of the Johns Hopkins Hospital*

	A	B	C	D	E	F	G	H	I
Age	Person-Years Exposed to Risk	Total Deaths in Period	Total Rate All Causes 1,000 B / A	Carcinoma Deaths in Period	Carcinoma Rate 1,000 D / A	Sarcoma and Other Malignant Deaths in Period	Sarcoma and Other Malignant Rate 1,000 F / A	All Malignant Deaths in Period	All Malignant Rate 1,000 H / A
0- 9	21678.5	491	22 65	..	0	11	0.51	11	0.51
10-19	20135.0	113	5.61	1	0.05	10	0.50	11	0.55
20-29	18315.0	251	13.70	7	0.38	18	0.98	25	1.37
30-39	15375.0	337	21.92	23	1.50	25	1.63	48	3.12
40-49	11480.0	442	38.50	65	5.66	22	1.92	87	7.58
50-59	7045.0	445	63.17	85	12.07	22	3.12	107	15.19
60-69	3265.0	311	95.25	81	24.81	10	3.06	91	27.87
70-79	950.0	152	160.00	28	29.47	1	1.05	29	30.53
80-89	100.0	18	180.00	3	30.00	..	....	3	30.00
90-99	5.0	1	200.00	..	....	..	....	..	....
Totals	98348.5	2561	26.04	293	2.98	119	1.21	412	4.19

necropsied population is large enough to be actuarially respectable in point of size. The 6,605 persons in it who died at known ages lived altogether a total of 213,192 years before they came to the "dead house." This is a sufficiently large figure to give fairly smooth death rates at ages. Taking all ages and all causes of death together, we get for the crude death rate in the necropsied population, per thousand person-years exposure to risk

$$\frac{6,605,000}{213,192} = 30.98$$

From Glover's tables the corresponding total rate for the general population of the Registration Area in 1910 is 19.42.[13] It is thus seen that if we consider only persons whose stay in a hospital is terminated by a necropsy they exhibit a death rate about 11 per thousand person-

13. Pearl (footnote 4, p. 199).

TABLE 11.—*Death Rates for Female Whites in the Necropsied Population of the Johns Hopkins Hospital*

Age	A Person-Years Exposed to Risk	B Total Deaths in Period	C Total Rate All Causes 1,000 B / A	D Carcinoma Deaths in Period	E Carcinoma Rate 1,000 D / A	F Sarcoma and Other Malignant Deaths in Period	G Sarcoma and Other Malignant Rate 1,000 F / A	H All Malignant Deaths in Period	I All Malignant Rate 1,000 H / A
0- 9	10030.0	385	38.38	..	....	10	1.00	10	1.00
10-19	8790.0	88	10.01	2	0.23	5	0.57	7	0.80
20-29	7620.0	146	19.16	3	0.39	11	1.44	14	1.84
30-39	5835.0	211	36.16	26	4.46	11	1.89	37	6.34
40-49	3690.0	218	59.08	52	14.09	12	3.25	64	17.34
50-59	1880.0	144	76.60	49	26.06	7	3.72	56	29.79
60-69	745.0	83	111.41	34	45.64	3	4.03	37	49.66
70-79	190.0	28	147.37	7	36.84	..	....	7	36.84
80-89	30.0	4	133.33	..	....	..	....	..	....
90-99	5.0	1	200.00	..	....	..	....	..	....
Totals	38815.0	1308	33.70	173	4.46	59	1.52	232	5.98

TABLE 12.—*Death Rates for Male Colored in the Necropsied Population of the Johns Hopkins Hospital*

Age	A Person-Years Exposed to Risk	B Total Deaths in Period	C Total Rate All Causes 1,000 B / A	D Carcinoma Deaths in Period	E Carcinoma Rate 1,000 D / A	F Sarcoma and Other Malignant Deaths in Period	G Sarcoma and Other Malignant Rate 1,000 F / A	H All Malignant Deaths in Period	I All Malignant Rate 1,000 H / A
0- 9	12482.0	464	37.17	..	....	2	0.16	2	0.16
10-19	11335.0	75	6.62	1	0.09	2	0.18	3	0.26
20-29	9675.0	257	26.56	3	0.31	3	0.31	6	0.62
30-39	7220.0	234	32.41	8	1.11	1	0.14	9	1.25
40-49	4800.0	250	52.08	20	4.17	3	0.63	23	4.79
50-59	2520.0	206	81.75	24	9.52	3	1.19	27	10.71
60-69	980.0	102	104.08	14	14.29	..	....	14	14.29
70-79	275.0	39	141.82	5	18.18	..	....	5	18.18
80-89	45.0	7	155.56	..	....	..	....	..	....
90-99	5.0	1	200.00	..	....	..	....	..	....
Totals	49337.0	1635	33.14	75	1.52	14	0.28	89	1.80

TABLE 13.—*Death Rates for Female Colored in the Necropsied Population of the Johns Hopkins Hospital*

Age	A Person-Years Exposed to Risk	B Total Deaths in Period	C Total Rate All Causes 1,000 B / A	D Carcinoma Deaths in Period	E Carcinoma Rate 1,000 D / A	F Sarcoma and Other Malignant Deaths in Period	G Sarcoma and Other Malignant Rate 1,000 F / A	H All Malignant Deaths in Period	I All Malignant Rate 1,000 H / A
0- 9	7901.5	381	48.22	..	....	4	0.51	4	0.51
10-19	6645.0	111	16.70	..	....	1	0.15	1	0.15
20-29	5235.0	171	32.66	4	0.76	1	0.19	5	0.96
30-39	3550.0	166	46.76	10	2.82	1	0.28	11	3.10
40-49	2005.0	143	71.32	24	11.97	4	1.99	28	13.97
50-59	895.0	79	88.27	16	17.88	3	3.95	19	21.23
60-69	330.0	34	103.03	8	24.24	1	3.03	9	27.27
70-79	100.0	12	120.00	2	20.00	..	....	2	20.00
80-89	25.0	3	120.00	..	....	..	....	..	....
90-99	5.0	1	200.00	..	....	..	....	..	....
Totals	26691.5	1101	41.25	64	2.40	15	0.56	79	2.96

years exposure, higher than the life table death rate of a general population. Of course, if we took the total hospital population, instead of that portion of it which comes to necropsy, the mortality rate would be expected to be considerably lower than the life table rate for a general population, because, as was pointed out in the paper preceding the present one in this series, people tend to die outside of hospitals more frequently than in them. Presumably the interposition of hospital treatment delays the advent of death for a good many of those who pass through its wards. But unfortunately the data are lacking for a precise

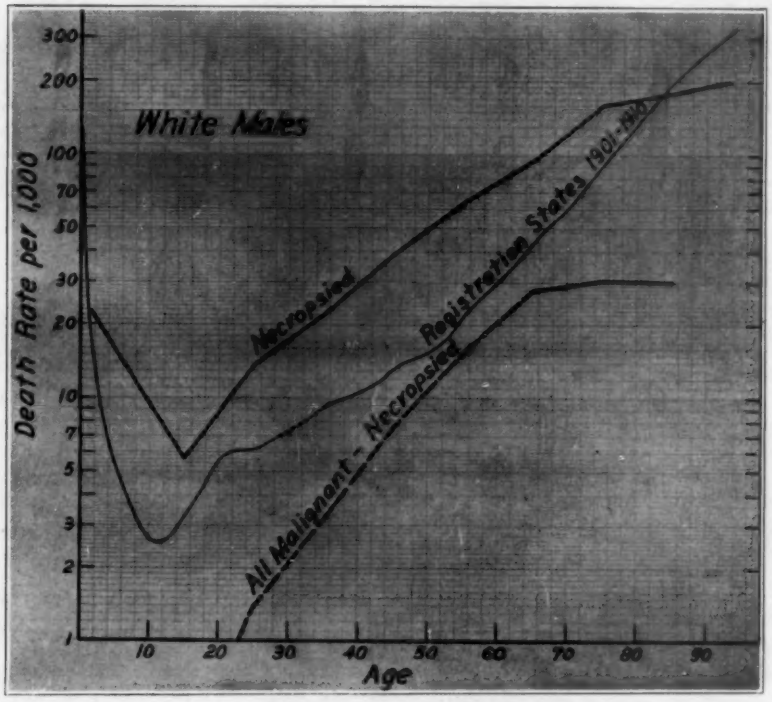

Chart 7.—Comparing the death rates at ages among white males in (*a*) the necropsied population as a whole, (*b*) the general population of the Registration States and (*c*) the portion of the necropsied population dying of malignant tumors.

actuarial evaluation of the benefits of medical or surgical treatment, in hospital or otherwise, in terms of duration of life. No hospital, so far as we are aware, has sufficiently extensive and accurate follow-up records of its patients to make this possible.

The difference between the death rate of 30.98 for the necropsied population and 19.42 for the general population may probably be most wisely taken as a rough measure of the extent to which those persons

who come to necropsy after hospital treatment are constitutionally inferior life insurance risks as compared with the average of the general population.

It is of interest to compare in some detail the death rates at ages in the necropsied population as a whole, with the life table death rates of a general population, and with that portion of the necropsied population which had some malignant tumor at death. These comparisons are made graphically in charts 7 to 10. In these charts the death rates for the total necropsied population, given in the *C* columns of tables 10 to 13,

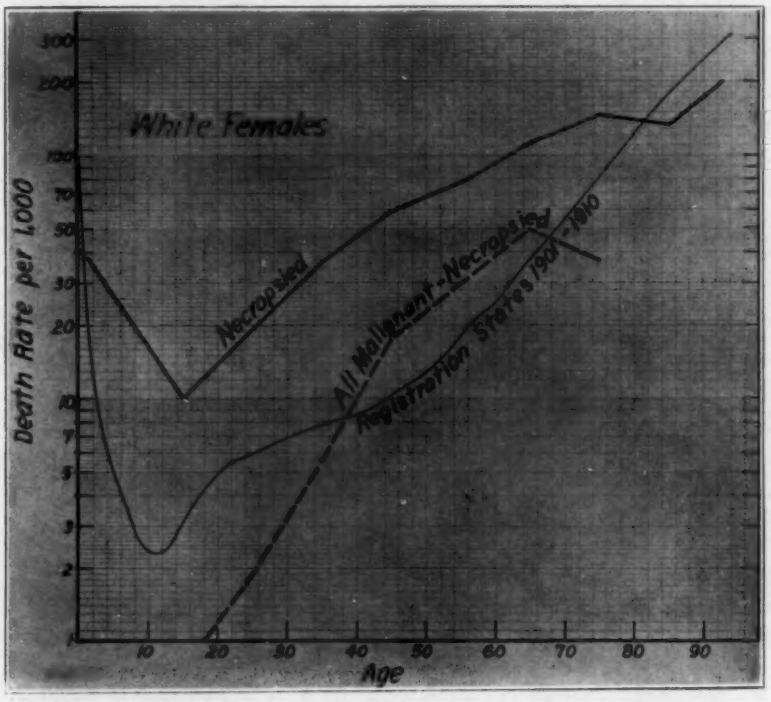

Chart 8.—Comparing the death rates at ages among white females in (*a*) the necropsied population as a whole, (*b*) the general population of the Registration States and (*c*) the portion of the necropsied population dying of malignant tumors.

are plotted as a solid line with angular turns. The life table death rates for the general population of the original Registration States in the period 1901-1910 (from Glover [14]) are plotted in each diagram as a solid, smoothly curved line. Finally, the "all-malignancy" rates, given in the *I* column of tables 10 to 13, are plotted as a dash line in each diagram.

14. Glover, J. W.: United States Life Tables, 1890, 1901, 1910, and 1901-1910, Washington, Government Printing Office, 1921.

These diagrams demonstrate clearly that the general form of the curve of death rates at ages in this necropsied population is closely similar to that exhibited by the corresponding curve for the general population. The two curves substantially parallel each other until advanced ages are reached. At first glance it might seem that there was a significant discrepancy in form in the earliest portion of the curves. The general population curves reach their minimum point at about 10 to 12 years of age, whereas the necropsied population curves seem to reach their minimum at an age of 4 or 5 years later. But this discrepancy

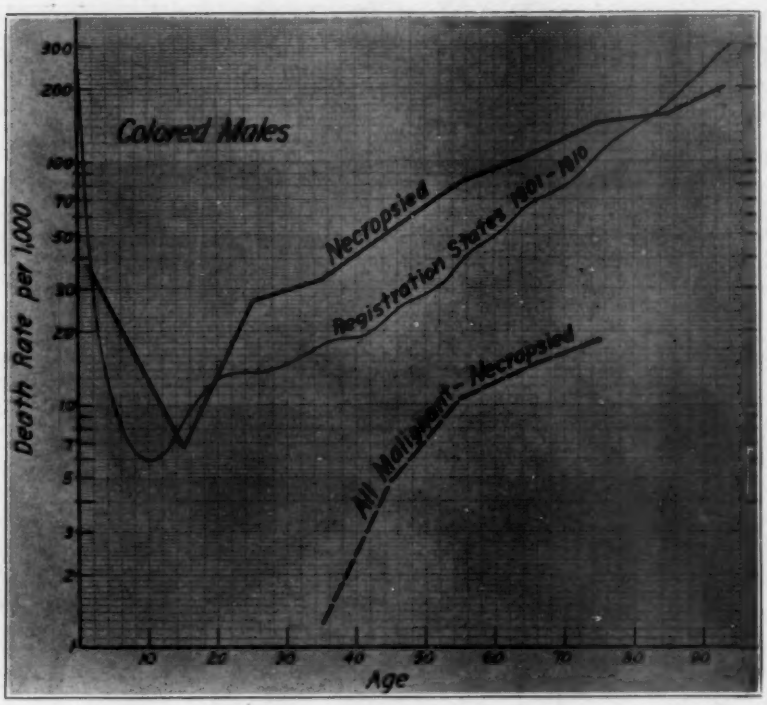

Chart 9.—Comparing the death rates at ages among colored males in (*a*) the necropsied population as a whole, (*b*) the general population of the Registration States and (*c*) the portion of the necropsied population dying of malignant tumors.

is mostly only apparent, and arises merely because the death rates for the necropsied population are calculated and plotted only at ten-year intervals. If we had these rates at yearly intervals, as is the case for the general population, it would be found that the minimum points would come at about the same age in both populations.

At all ages up to about 80 the death rate curve for the necropsied population lies above that for the general population. This is what would be expected, in view of the higher total death rate at all ages

and from all causes in the necropsied population which has already been discussed. The excess mortality of the necropsied over the general population is more marked in females than in the males, in both races. At all ages up to about 70 the females in the necropsied population show *higher* death rates at ages than do the males in the same population. This is, of course, a complete reversal of what is normally found in a general population, where female death rates are *lower* than male death rates, at practically all ages. In both sexes, the death rate curve for the necropsied population is closer to the curve for the general population in the colored

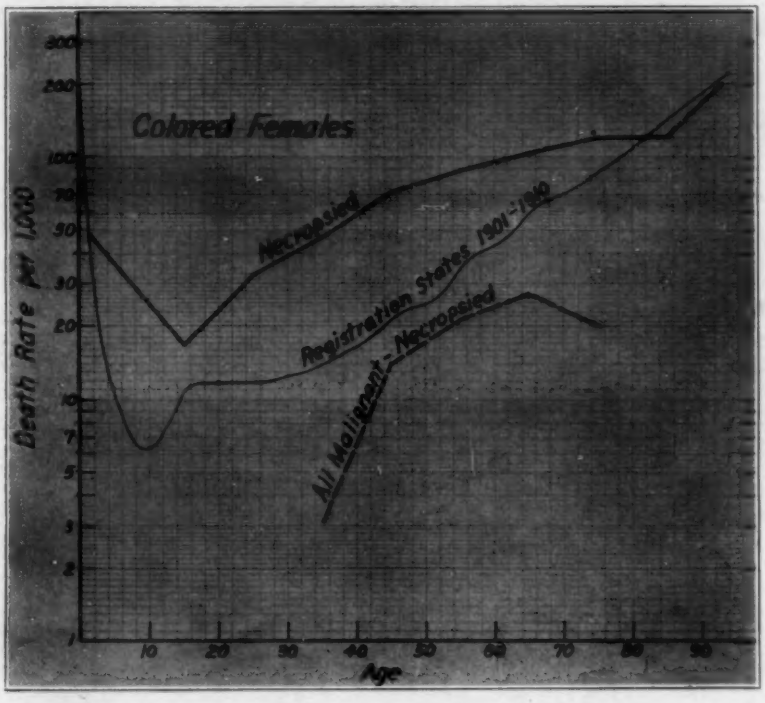

Chart 10.—Comparing the death rates at ages among colored females in (*a*) the necropsied population as a whole, (*b*) the general population of the Registration States and (*c*) the portion of the necropsied population dying of malignant tumors.

group than in the white. The colored are less differentiated from the general population than the whites.

Turning now to the death rates of the malignant portion of the necropsied population we note that the slope of this "all malignant" curve is steeper in all cases than the corresponding portion of the curves for both the total necropsied and the general population, up to about age 50. From there on to about age 65 the slope of the "all malignant" curve is substantially the same as that of the other two curves. This means,

remembering that the diagrams are plotted on an arithlog grid which guarantees the quantitative comparability of slopes, that during this period from about 50 to 65, when cancer death rates are generally at a maximum, they are following the same law of change relative to time and to senescence that deaths in general follow. Or, put in another way, cancer behaves in this age period like the other "men of death," from a mathematical point of view. It has no particular statistical peculiarities of its own.

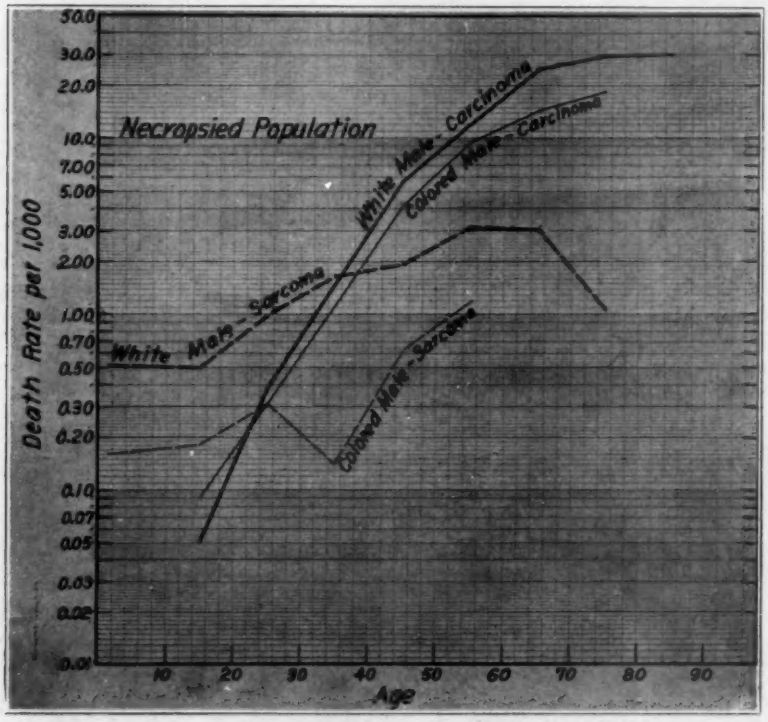

Chart 11.—Comparing the death rates at ages among male persons for (*a*) whites dying of carcinoma, (*b*) colored dying of carcinoma, (*c*) whites dying of sarcoma (or other malignant tumor, not carcinoma) and (*d*) colored dying of sarcoma.

It is of some interest to note from chart 8 that the "all malignant" rates in the white female portion of the necropsied population are actually higher than the death rates in a fairly comparable general population, between the ages of about 38 and 68. This emphasizes the poorness of the life risk which inheres in a white woman who is brought to a hospital because of a malignant growth.

Except in the case of colored males, death rates from malignant tumors do not appreciably increase after about age 65 in this necropsied

population, though it must always be remembered that the death rates at these higher ages are based on such meager numbers that any conclusion regarding them must be made with great caution and reserve. A striking difference between colored and white "all malignant" death rate curves, aside from the fact that the white curves are at all ages absolutely higher than the colored, is the lag of the colored curves. They get started only at higher ages than in the whites. At age 40 the white males in the necropsied population have an "all malignant" death rate of approximately 5 per thousand person-years exposure. But the colored males

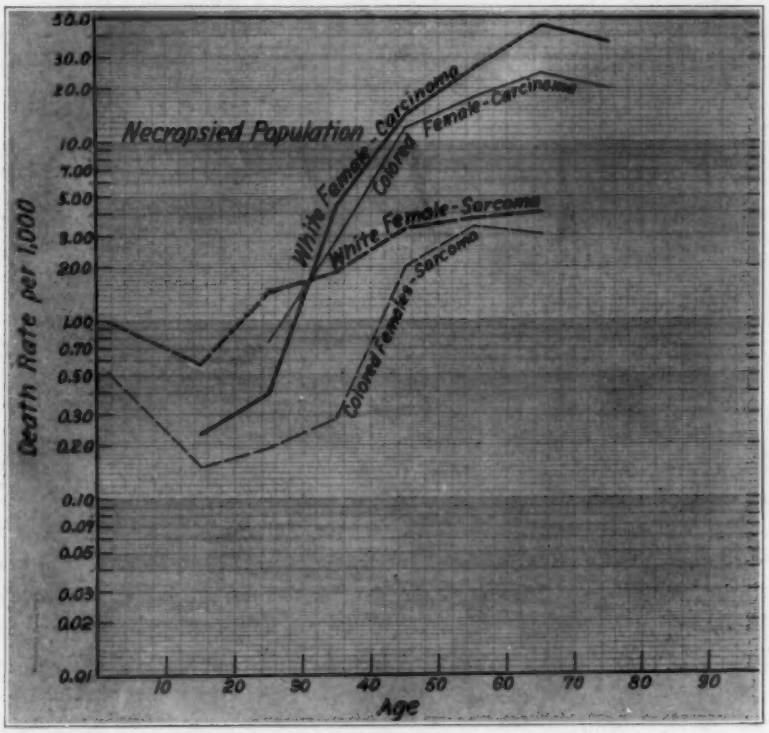

Chart 12.—Comparing the death rates at ages among female persons for (*a*) whites dying of carcinoma, (*b*) colored dying of carcinoma, (*c*) whites dying of sarcoma (or other malignant tumor, not carcinoma) and (*d*) colored dying of sarcoma.

attain a rate of 5 per thousand only at about age 46. In the white females the "all malignant" rate is 20 per thousand at age 48, while in the colored females it is not so much per thousand until approximately age 53, or five years later.

Charts 11 and 12 present graphically another aspect of the case. Chart 11 pertains to males only, and compares the carcinoma and

sarcoma life table death rate curves in the two broad racial groups, white and colored. Chart 12 does the same thing for females.

These diagrams (charts 11 and 12) again show as their first striking result that the death rates for the colored, from both carcinoma and sarcoma, are lower than those for the whites, at all ages, except those prior to about 30 in the case of carcinoma. But also these diagrams show clearly that this racial difference is much greater relatively for sarcoma than for carcinoma.

The general form of the curves for carcinoma is obviously quite different from that for sarcoma. The former rises steeply with age, taken as a whole. The latter rises with age, to be sure, but at a much more leisurely pace.

DISCUSSION AND SUMMARY

It is not our purpose to attempt any broad biologic or pathologic deductions from our study of malignancy in a necropsied population until the study has proceeded much further than it so far has. Therefore, all that we shall do in bringing the present contribution to a close is to summarize briefly the more important observations, as to fact, which are set forth in detail in the body of the paper.

It is well, in the first place, to emphasize again that the original, first-hand material here presented comes from the necropsy experience of one hospital only. This means that it cannot be regarded as a random sample of human beings in general. It must for the present be discussed from somewhat the same point of view that, for example, a unique specimen of fossil man has to be.

The outstanding merit of the basic material is its fundamental *accuracy*. In the data about malignant tumors in this paper there inheres a kind of certainty which can never be achieved from the official mortality statistics of a general population. Every single figure in our original tables rests on a careful, thorough necropsy made by a trained and expert pathologist. The contrast, in respect of accuracy, between such data about cancer, and the diagnoses of the general practitioner which are recorded on official death certificates is great. The advantages of the present material in this respect go a long way toward offsetting its deficiencies in other statistical respects.

The following results seem to be established with a high degree of probability by the data here presented:

1. In a total of 6,670 necropsies some form of malignant tumor was found in 12.2 per cent of the cases. Such tumors do not appear from official vital statistics to occur so frequently as this in the general population.

2. In this necropsied population carcinoma occurred much more frequently than did malignant tumors which were not carcinomas. This

material agrees with other hospital and necropsy data in indicating that from 22 to 25 per cent of cases of malignancy, taken at random, will be noncarcinomatous in character.

3. In this necropsied population malignant tumors of all sorts taken together occur from two to three times more frequently relatively among white persons than they do among colored persons. This racial difference is much more marked relatively for malignant tumors which are not carcinomatous (i. e., in the sarcoma and other groups) than it is for carcinomas. A careful critical examination of the most trustworthy available statistical data for general populations leads us to conclude that, *in general*, malignant new growths occur with considerably greater frequency in the white race than in the colored, in the United States. All lines of evidence concur in support of this conclusion—necropsy records, age corrected death rates for general populations, and death ratios specific for age and sex. The only apparently significant exception to this general conclusion is found in the fact that, during the child-bearing ages, colored females exhibit a higher incidence of malignancy than do white females. The generally less frequent occurrence of malignant neoplasms in the negro may indicate a lower susceptibility of truly genetic, racial origin, reflecting a real biologic differentiation of colored from white, in this respect. But one should be cautious about drawing such a conclusion on the basis solely of the evidence now available.

4. Malignant tumors of all kinds, taken in the aggregate, tend to occur a little more frequently, relatively, among females than they do among males in this necropsied population, but this tendency is small in magnitude and disappears entirely in the sarcoma group.

5. In this necropsied population, in both the carcinoma and sarcoma groups, the distributions of the individuals in respect of age at death are symmetrical about their mean points, within the margin of error reasonably to be expected from random sampling.

6. In this necropsied population persons having carcinoma die at a much higher average age than those having sarcoma (or other non-carcinomatous malignant tumor). This difference is of the order of 16 to 20 years, the carcinoma deaths generally occurring at an average age around 50 to 55. But there is, in all groups, a higher degree of variability in age at death from malignancy.

7. The colored persons in this necropsied population who die with malignant tumors, tend to do so at an earlier age, on the average, than do whites. The only exception is in the case of the female sarcomatous groups.

8. Cancerous females, so far as may be judged from this necropsied population, tend to die at an earlier age, on the average, than do cancerous males.

9. The relationships of the races and sexes in respect of age at death from malignant tumors stated in the two preceding paragraphs are also true of the general population of the Registration States, as judged from official vital statistics.

10. The crude death rate of the necropsied population, taking all ages and all causes together, is 30.98 per thousand person-years exposure to risk, as against 19.42 for the general population in 1910. The reason for the excess is discussed in the body of the text.

11. Actuarial treatment of the data from this necropsied population leads to the general conclusion that the form of the life curve for such a population is substantially similar to that of the life curve for a general population, though its absolute position in space is different. The life curves for the persons in this necropsied population dying with malignant tumors are characteristically different from the "all causes" curves.

THE BILIRUBIN CONTENT OF GALLBLADDER BILE IN CHOLECYSTIC DISEASE *

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One of the functions of the gallbladder, which has been demonstrated experimentally, is to concentrate the bile secreted by the liver. In experimental, acute, specific cholecystitis, this concentrating activity is diminished in proportion to the extent of the pathologic changes. Although the clinical manifestations of gallbladder disease may be attributed to a wide variety of pathologic processes, certain types of cholecystic disease may be expected to show a definite alteration in the concentrating activity of the gallbladder. The failure of a definite correlation of the lesions in the gallbladder with the clinical history, symptoms and prognosis led C. H. Mayo to suggest a functional basis for the comparison of gallbladder diseases. Following this suggestion we have examined grossly and microscopically 105 gallbladders removed at operation. The bilirubin content of the gallbladder bile was determined by the van den Bergh [1] method, and the variations in concentration were compared with the pathologic changes in the wall or contents of the gallbladder.

The difference in the character of the bile secreted by the liver and of that found in the gallbladder led Kemp [2] to suggest that the bile was concentrated in the gallbladder. Hohlweg [3] demonstrated that by the gallbladder's absorption of water, it could concentrate the bile secreted during the intervals between digestion, so that the 40 cc. of bile found in the gallbladder represented from 240 to 400 cc. from the liver. Rous and McMaster [4] ligated the common bile duct of dogs and intubated the

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1. Van den Bergh, A. A. H.: La recherche de la bilirubin dans le plasma sanguin, Presse méd. **1**:441-443, 1921.

2. Kemp, G.: Experimental Researches on the Function of the Mucous Membrane of the Gallbladder, Principally with Reference to the Conversion of Hepatic to Cystic Bile, Proc. Roy. Soc. London **8**:133-140, 1856-1857.

3. Hohlweg, H.: Ueber Störungen der Salzsäurcabscheidung des Magens bei Erkrankungen und nach Extirpation der Gallenblase, Deutsches Arch. f. klin. Med. **108**:255-276, 1912.

4. Rous, Peyton, and McMaster, P. D.: The Concentrating Activity of the Gallbladder, J. Exper. Med. **34**:47-73, 1921.

hepatic ducts, so that the bile secreted by a portion of the liver went into the gallbladder, while that secreted by the remainder of the liver passed into the bile duct, to which a rubber balloon was attached. Control observations were made on the uniformity of the pigment content of the bile secreted from different portions of the liver. It was found that the pigment content of each cubic centimeter of bile in the gallbladder may be ten times greater than that of the bile secreted into the duct, showing that the bile in the gallbladder had been greatly concentrated. Mann and Bollman [5] ligated the common bile duct in dogs and observed that signs of icterus, that is, bile pigment in the blood, urine, sclerotics and mucous membranes, did not develop for from thirty-six to forty-eight hours after operation. When the gallbladder was removed at the same time the common duct was ligated, bile pigment was definitely demonstrated in the blood and urine within three hours after operation, and the sclerotics and mucous membranes were definitely yellow within twenty-four hours. The difference in the rate of accumulation of bile pigment was considered evidence of the gallbladder's ability to concentrate the bile secreted by the liver, since a great increase in the concentration of the pigment in the gallbladder bile occurred following ligation of the common bile duct. Bollman, Mann and DePage [6] induced specific cholecystitis in dogs by the intravenous injection of chlorinated soda. In animals in which the entire gallbladder appeared diseased, jaundice developed as rapidly as in animals in which the gallbladder was removed and the common bile duct was ligated similarly. Animals with milder disease of the gallbladder developed jaundice less rapidly, and animals with but slight disease developed jaundice at the same rate as normal animals, following ligation of the common bile duct. These facts clearly demonstrate that the gallbladder's function of concentrating the bile is impaired or may be totally lost, if the organ is acutely inflamed.

Jones [7] found marked increases in bile pigment in the duodenal contents obtained by Lyon's method, in cases of gallbladder disease. This abnormally high concentration of bile pigments was less marked in cases of cholelithiasis than in cases of uncomplicated cholecystitis. He attributed his results to stasis of bile in the gallbladder in cholecystic disease and to hepatic changes which may be associated with this condition, although increased destruction of blood might also be a factor in some

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5. Mann, F. C., and Bollman, J. L.: The Relation of the Gallbladder to the Development of Jaundice Following Obstruction of the Common Bile Duct, J. Lab. & Clin. Med. **10**:540-544, 1924-1925.

6. Bollman, J. L.; Mann, F. C., and De Page, Pierre: The Effect of Specific Cholecystitis on the Bile Concentrating Activity of the Gallbladder, J. Lab. & Clin. Med. **10**:544-547, 1924-1925.

7. Jones, C. M.: Blood Pigment Metabolism and Its Relation to Liver Function, Arch. Int. Med. **29**:643-668 (May) 1922.

of his cases. However, Fitz and Aldrich [8] examined the bile from seventy-two gallbladders removed at operation for cholecystic disease. They found that gallbladder bile in cases of cholecystitis with gallstones tended to be less pigmented, of lower specific gravity and less rich in nitrogen than the bile in cases of cholecystitis without stones, and that in acutely inflamed gallbladders the bile was often cloudy. Because of the great variation encountered in the composition of the individual specimens of bile studied, they could draw only general conclusions and were unable to correlate satisfactorily their data with clinical and operative observations. The cholesterol content of the bile was even more varied, so that it appeared that the condition of the gallbladder was not related to the cholesterol content of the bile.

METHOD

The preoperative regimen of the patients in this series afforded fairly well standardized conditions with reference to the possible emptying of the gallbladder. In the chronic cases food had not been taken for fifteen hours prior to operation and in the acute cases conditions of feeding were similar except that in a few cases food had not been taken for a longer period.

As soon as the gallbladders were removed they were taken to the laboratory, and opened, and any unusual feature in the wall or contents was noted. Blocks of tissue were cut from the diseased areas and immediately fixed in 10 per cent formalin. Frozen sections were made and stained with hematoxylin and eosin. A few cubic centimeters of the bile of these gallbladders was placed on ice for the chemical examination. Within a few hours the bile was diluted and the number of milligrams of bilirubin contained in 100 cc. of the bile was determined by the van den Bergh method. This was accomplished by diluting the bile with 50 per cent alcohol until the van den Bergh reagent gave a color approximately like that of van den Bergh's original standard solution. The color comparison was then made with the Dubosque colorimeter and the calculations were made according to the dilutions employed.

RESULTS

The pathologic changes seen in the wall of the gallbladder or in its contents in any of the conditions of this viscus are so varied that only a general description can be made and a general name given to the changes. In the gallbladder, as in any other organ, pathologic conditions change, and one type of disease may merge into another without any line of

8. Fitz, Reginald, and Aldrich, Martha: Clinical Observations on Certain Constituents of Bile, J. A. M. A. **79**:2129-2132 (Dec. 23) 1922.

demarcation. On this account, only the salient features of the disorders are mentioned, with the realization that a sharp definition of cholecystic disease is impossible, particularly in the milder types. There were twelve types of gallbladder disease in this series according to the gross and microscopic pathologic diagnosis as shown in the table.

Slight Chronic Cholecystitis.—In cases diagnosed as slight chronic cholecystitis, the gallbladder revealed the slightest changes of any removed at operation. There were a few inflammatory cells (lymphocytes) in the mucosa or its stroma (fig. 1, *b*). Occasionally the epithelium was desquamated in a few areas, and it was not uncommon to find deposits of yellow pigment in the epithelial cells of the lining. This pigment deposited mostly in the cytoplasm nearest the lumen of the gall-

Bilirubin Content of the Gallbladder Bile in Various Types of Gallbladder Disease

Diagnosis	Cases	Bilirubin Content in Gallbladder Bile (Mg. for Each 100 Cc.)		
		High	Low	Average
Slight chronic cholecystitis	5	65.0	11.0	39.4
Chronic cholecystitis	15	66.0	4.1	35.2
Chronic cholecystitis with papillomas	8	121.0	11.0	49.1
Chronic cholecystitis with "strawberry" gallbladder	7	66.0	2.2	31.5
Chronic cholecystitis with stones	50	90.0	0.0	21.1
Chronic cholecystitis with stones and papillomas	2	55.0	33.0	44.0
Chronic cholecystitis with stones and "strawberry" gallbladder	4	27.5	4.4	14.8
Chronic cholecystitis with stones (cystic gallbladder)	4	0	....	.....
Acute cholecystitis or chronic cholecystitis (caramel bile) with stones	1	0	....	.....
Empyema of the gallbladder	5	4.4	....	0.88
Acute gangrenous cholecystitis with stone	1	1.1	....	1.1
Chronic cholecystitis, contracted gallbladder	3	5.2	....	2.7

bladder was less concentrated deeper in the columnar cells. Aschoff [9] recently described it as an apparently "normal" constituent of the epithelium of the gallbladder.

Chronic Cholecystitis.—The gross changes in the cases of chronic cholecystitis were usually slight thickening of the gallbladder wall, and occasionally edema of the mucosa or stroma. Microscopically the changes were essentially like those in the former group but increased in amount. There was fibrosis of the wall of the gallbladder, beginning usually as an increase of the intermuscular connective tissue. Occasionally the mucosa and its stroma and the adjacent intermuscular connective tissue were infiltrated with lymphocytes, plasma cells and eosinophils. We have seen gallbladders in this group in which the connective tissue was dense and the rugae of the mucosa apparently decreased in height (fig. 2, *a* and *b*).

9. Aschoff, Ludwig: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

Chronic Cholecystitis with Papillomas.—Marked hypertrophy of the epithelium lining the gallbladder is the most striking characteristic of chronic cholecystitis with papillomas.[10] We have occasionally found this type of epithelium associated with other kinds of cholecystitis. Kaufmann [11] believes that the older a person grows the more papillomatous the gallbladder epithelium tends to become. Is this change of the epithelium due to age or to the inflammatory changes in the gallbladder mucosa which many times accompany increasing years? Of the ten patients with papillomas in this series, seven were in the fifth decade of life, two in the sixth and one in the seventh. The papillomas were

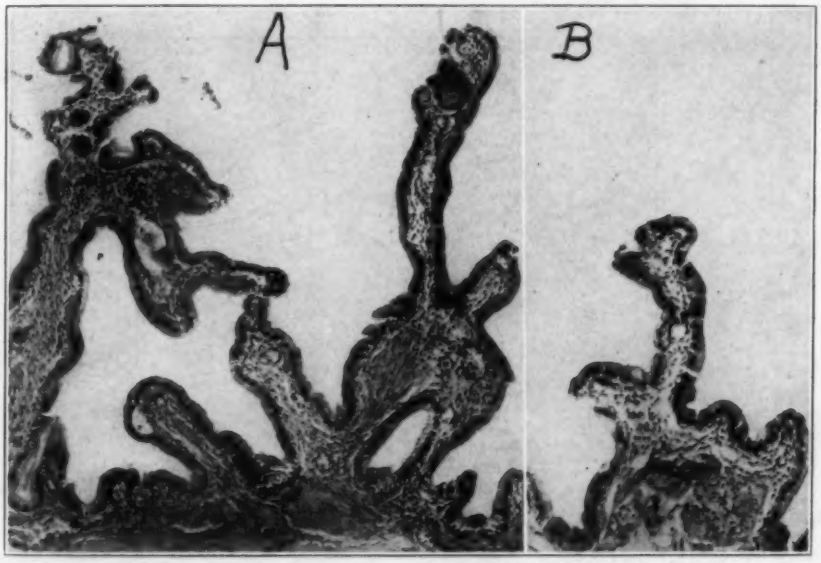

Fig. 1.—*A*, hypertrophic rugae in chronic cholecystitis with papillomas. × 60. *B*, slight chronic cholecystitis with some lymphocytic infiltration. × 60. It should be noted that the height of the rugae is about twice as great in *A* as in *B*.

grossly visible and varied from 1 to 3 or 4 mm. in diameter. The number in one gallbladder varied from one to fifteen or twenty. Occasionally cholesterol was deposited in one or more papillomas. Inflammatory cells already described were noted in the gallbladder wall. Pigment in the lining epithelium was usually prominent. The rugae of the mucosa in most cases were between one and two times longer than those in other types of cholecystitis (fig. 1). This greater length of the folds markedly

10. Erwin, H. C., and MacCarty, W. C.: Papilloma of the Gallbladder, Ann. Surg. **61**:725-729, 1915.

11. Kaufmann, Eduard: Lehrbuch der speziellen pathologischen Anatomie, Berlin, Walter de Gruyter & Co., 1922, pp. 767-768 and 771-782.

increases the surface of the gallbladder epithelium. Papillomas of the gallbladder are composed of loose fibrous connective tissue stroma covered by columnar epithelium.

Chronic Cholecystitis with "Strawberry" Gallbladder.—The deposits of cholesterol beneath the mucosa described by MacCarty [12] are grossly distinguished by yellow flecks of cholesterol beneath the lining epithelium. This condition can vary from a few small deposits frequently near the cystic duct to widespread accumulations throughout the lining of the gallbladder. Microscopically the space formerly occupied by lipoid is visible in fixed tissue preparations in the stroma just beneath the epithelium.

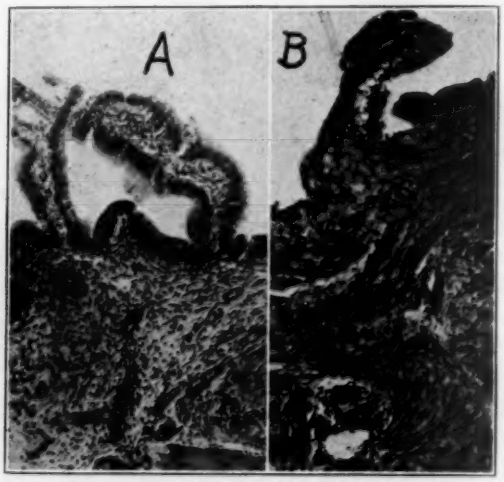

Fig. 2.—*A*, a type of chronic cholecystitis characterized by infiltration of the stroma and intermuscular connective tissue with inflammatory cells. × 60. *B*, more advanced chronic cholecystitis with increase in fibrous connective tissue of the wall, infiltration of lymphocytes and desquamation of the epithelium. × 60.

Chronic Cholecystitis with Stones and Papillomas or "Strawberry" Gallbladder.—Gallbladders containing papillomas or with cholesterosis [13] may be associated with stones. The walls of the organ with this associated complication were, grossly and microscopically, the same as in the cases without cholelithiasis. In fact one striking feature of cholecystic disease is that a gallbladder can contain many stones and still show but slight changes in the wall. The type of epithelium noted in cholecystitis

12. MacCarty, W. C.: The Frequency of "Strawberry" Gallbladders, Ann. Surg. **69**:131-134, 1919.

13. Mentzer, S. H.: Cholesterosis of the Gallbladder, Am. J. Path. **1**:383-388, 1925.

with stones varied from low rugae covered by low columnar or cuboidal cells to tall folds suggestive of those already described in cholecystitis with papillomas. Desquamation of the lining epithelium is frequently associated with cholelithiasis. The connective tissue of the wall of the gallbladder with stones is frequently changed from a loose to a dense texture. Edema of the intermuscular tissue and inflammatory cells invading the walls may be present.

Acute Cholecystitis Superimposed on Chronic Cholecystitis, with Stones and "Caramel" Bile.—In one case acute cholecystic disease was apparently engrafted on chronic cholecystitis associated with many gallstones. The bile in this case was designated "caramel" bile. The viscid character, the dark brown color and the crystals of cholesterol floating in the bile warranted this term. The wall of the gallbladder was much thickened, the blood vessels were engorged, and there were hemorrhages of the mucosa and submucosa with an accompanying solution of tissue. A few polymorphonuclear leukocytes were seen in smears of the bile, and lymphocytes were seen in the wall. A bit of liver tissue attached to the gallbladder revealed infiltration with lymphocytes, endothelial leukocytes, plasma cells and a few polymorphonuclear leukocytes. This condition is probably an early stage of empyema of the gallbladder.

Empyema of the Gallbladder.—The pathology of empyema of the gallbladder is common knowledge. The stoppage of the cystic duct, which is a feature of this disorder, is usually from obstruction by one or more stones.

Hydrops of the Gallbladder (Cystic Gallbladder).—Aschoff believes that hydrops of the gallbladder is always an infectious inflammatory disease and develops from empyema. Cholelithiasis is usually present, although the same disorder may be brought about by closure of the cystic duct from other causes. The signs of gallbladder disease are similar in hydrops and empyema except that in the latter there are signs of acute disease, usually indicated by polymorphonuclear leukocytes, and also more extensive disease, evidenced by ulceration of the mucosa and muscle coats. Thrombosis of the arteries, with hemorrhage and foreign body giant cells, is sometimes seen. Gangrene of the gallbladder may be an end-result of this disorder. In one case in this series, aside from the usual cholelithiasis, carcinoma of the cystic duct was seen.

Chronic Cholecystitis with Contracted Gallbladder.—The type of chronic cholecystitis with contraction of the gallbladder is probably the acme of chronic inflammatory change in this organ. Grossly the gallbladder is small, with a fat infiltrated serous coat, and it is frequently buried in adhesions. The walls are extremely fibrous and infiltrated with cells significant of chronic inflammatory disease. The lining epithelium

is atrophic, and frequently its characteristic rugae are replaced by irregular sprigs of epithelium interspersed with areas of desquamation. The viscus contains one or more stones and a few cubic centimeters of bile. If acute inflammation develops later, polymorphonuclear leukocytes, areas of hemorrhage and engorged blood vessels will be seen in the wall.

COMMENT

The concentration of bile is a function of the gallbladder, and it might be expected that this activity would be interfered with according to the pathologic changes in that organ. There is a definite relationship beween the bilirubin content of the gallbladder bile and certain pathologic conditions in the gallbladder. This is to be noted in the cystic gallbladder, in empyema of the gallbladder and in acute inflammation of the gallbladder, all of which are associated with little or no bilirubin in the gallbladder bile. In these conditions the whole organ is diseased and the absorbing surface is therefore extensively damaged. On the other hand, gallbladders with papillomas and the associated hypertrophic rugae revealed the greatest concentration of bile in this series. Such organs appear to possess the greatest amount of absorbing surface, because of the epithelial covering of the papillomas and the hypertrophic rugae. If this epithelium possesses its normal function, it is not surprising that hyperconcentration of bile should take place in these organs.

In other types of cholecystic disease the entire organ is not necessarily involved. There may be hyperfunctioning areas, impaired areas and normal areas in the viscus. The concentration of bile, being dependent on the whole organ, does not show any marked changes definitely comparable with the type of disease present. In general, however, the more extensive the damage to the gallbladder, the less was the concentration of bilirubin in the gallbladder bile.

The presence or absence of cholelithiasis does not seem to have any direct bearing on the concentrating activity of the gallbladder so long as the stones remain free in the organ, for this function is dependent on associated changes in the gallbladder wall and complicating conditions. Constriction of the common duct gives rise to an increased concentration of bile in the gallbladder in uncomplicated conditions, but more frequently associated changes in the gallbladder and biliary ducts are superimposed so that other changes are found.

The color of the bile is not always an index of its bilirubin content. The discrepancy between the appearance and the concentration is particularly marked in the thickened dirty bile which is uniformly low in bilirubin content. The presence of such bile seems to indicate impairment of concentrating ability of the gallbladder.

SUMMARY

The bilirubin content of bile from 105 diseased gallbladders was compared with the anatomic changes in these organs. The amount of bilirubin in the bile was considered an index of the activity of the gallbladder in the concentration of the bile. Certain pathologic conditions of the gallbladder are accompanied by definite alterations of the bilirubin content of the gallbladder bile. In these conditions the organ as a whole is affected. In acute inflammatory cholecystic disease, empyema, hydrops (cystic gallbladder) and contracted gallbladder, the concentrating activity is absent. In cholecystitis with papillomas, associated with hypertrophic rugae, the concentration of bile is definitely increased. Between these two extremes a wide variation of the bilirubin content is found.

EFFECT OF REPEATED INJECTIONS OF PARATHYROID EXTRACT ON CALCIFICATION OF OSTEOID TISSUES *

WILHELM HUEPER, M.D.

CHICAGO

Osteomalacia, rickets, ostitis fibrosa and senile atrophy of the bones are diseases which are characterized by disturbances in the calcification of the bones. Their causation is not known, but irregularities in the function of certain glands of internal secretion (suprarenal gland, ovary, thymus, thyroid) are considered by many authors to be causative factors in the genesis of these diseases. Hyperplastic proliferations of the parathyroid glands which are not rarely found in conjunction with these pathologic conditions of the bones are, according to the interpretation by the majority of the observers, compensatory hyperplastic formations of the glands representing attempts to reestablish normal conditions in the disturbed mineral metabolism. On account of their absence in a large number of these cases, they are usually not regarded as the cause of the decalcification taking place in the bones (Hoffheinz,[1] Dibbelt,[2] Danisch,[3] Kerl [4]). Moreover, experiments of Dieterich [5] and others furnish some important substantiation of this conception. These authors report that the calcification of the osteoid callus is incomplete and slowed after the removal of the parathyroid glands, observations which also agree with the well known theory of Erdheim [6] concerning the normal function of the parathyroid glands.

In a previous paper I presented a description of the pathologic alterations produced in the organs of dogs by the accumulative effect of

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* From the Pathological Department, Loyola University, School of Medicine.

1. Hoffheinz: Ueber Vergrösserungen der Epithelkörperchen bei Ostitis Fibrosa und verwandten Krankheitsbildern, Virchows Arch. f. path. Anat. **256**:705, 1925.

2. Dibbelt: Die Bedeutung der Kalksalze für die Schwangerschafts-und Stillperiode, Beitr. z. path. Anat. u. z. allg. Pathol. **48**:147, 1910.

3. Danisch: Die menschlichen Epithelkörperchen in Senium, Frankfurt. Ztschr. f. Path. **32**:188, 1925.

4. Kerl: Zur Frage der Epithelkörperchenhyperplasien bei Osteomalazie und Osteoporose, Deutsche med. Wchnschr. **51**:1271, 1925.

5. Dieterich: Die parathyreoide Callusbildung, Arch. f. klin. Chir. **136**:388, 1925.

6. Erdheim: Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis, Beitr. z. path. Anat. u. z. allg. Pathol. **33**:158, 1903; and **35**:366, 1904.

repeated injections of parathyroid extract.[7] In the present communication I will report the results of a study of the influence of repeated injections of parathyroid extract (Collip), given over a longer period of time and in proper intervals to avoid accumulative effects, on the calcification of osteoid tissue.

EXPERIMENT

Technic.—Six cats, three 2 years old and three 6 months old, were used in the experiment. They were fed with milk and meat. The radius and the ulna of the left foreleg in each of them were fractured by hand under ether anesthesia. One of the old cats (no. 6) and one of the young ones (no. 5) were used as controls and did not receive any further treatment. The other four (nos. 1 and 3 young cats, and nos. 2 and 4 old cats) received an injection of 15 units of parathyroid extract (Collip) intramuscularly twice a week for four weeks, beginning the day after the operation. A roentgenogram of the fractured leg was also made on this day and again at the end of each week following operation, for observation of the development of the callus formation, in regard to the date of its first appearance, its amount and its degree of calcification. At the end of the fourth week the cats were killed. The internal organs were studied for eventual pathologic changes produced by the prolonged treatment with parathyroid extract, while the fractured bones were examined for histologic evidence of differences in the callus formation of the treated cats and in that of the control cats.

Results.—During the whole period of observation the treated cats did not show any clinical symptoms of an injurious effect due to the injected hormone. Loss of appetite, vomiting, diarrhea and stupor, the signs of parathyroid hormone poisoning, were not observed. However, it must be recorded that the treated animals appeared to be somewhat more quiet and to use the broken extremity more freely than the control cats.

The roentgenograms which were interpreted by Warren Furey and John Zingrone (Roentgenological Department, Mercy Hospital, Chicago) yielded the following observations.

The roentgenograms of the forelegs of the six animals, taken one day after the operation, show typical transverse fractures of the ulna and the radius in the middle of the shaft, without deviation of the fragments.

The roentgenographic examination of the young animals 1 and 3 fourteen days after the fractures shows approximately 5 per cent more callus formation than that of the control animal 5, with 5 per cent new bony growth. The pictures of the older animals 2, 4 and 6, taken at the same date, show a considerable callus formation but not any difference in its amount when pictures of animals 2 and 4 are compared with that of animal 6.

The roentgenograms taken three weeks after the fracture show about 15 per cent more callus in animals 1 and 3 compared with that of 5, while those of cats 2 and 4 show approximately 7 per cent more new bony growth than that of the control animal 6.

The roentgenograms taken four weeks after the fracture show approximately 25 per cent more callus in the injected animals 1 and 3 and 2 and 4, respectively, than those of the control animals 5 and 6. The bony union of the fractures of the animals 1, 2, 3 and 4 was completed to approximately 75 per cent, while control animals 5 and 6 had a bony union of only about 50 per cent (figs. 1, 2, 3 and 4).

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7. Hueper, Wilhelm: Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

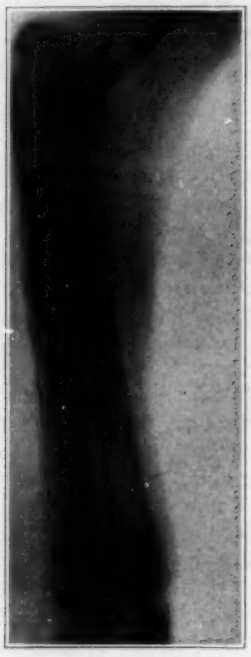

Fig. 1 (cat 1).—Injection performed; four weeks after fracture.

Fig. 2 (cat 5).—Control; four weeks after fracture.

Postmortem Examination.—This did not reveal any gross pathologic alterations of the internal organs. The histologic study of these organs (thyroid, parathyroid, thymus, lungs, heart, aorta, liver, pancreas, spleen, kidney, suprarenal, stomach, duodenum, ovary, skeleton muscle) yielded normal observations in cats 2, 5 and 6. The heart muscle of cats 1, 3 and 4 showed a few small necroses invaded and surrounded by leukocytes. Similar alterations were present in the cortex of the suprarenal gland of cat 1.

The results of my study of the fractured bones may be summarized as follows:

Figure 3

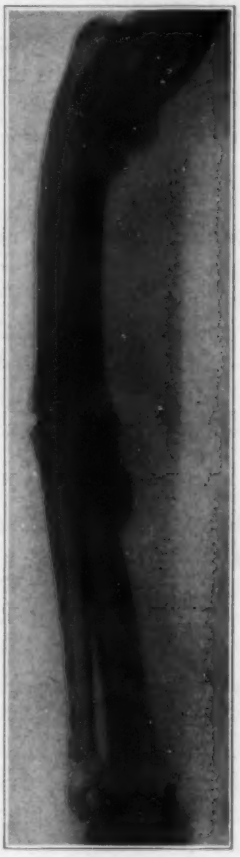

Figure 4

Fig. 3 (cat 2).—Injection performed; three weeks after fracture.
Fig. 4 (cat 6).—Control; three weeks after fracture.

The periosteal as well as the endosteal callus of the animals that received injections was composed mainly of spongious bone, osteoid tissue and calcified cartilage and only to a minor degree of fibrous tissue. The callus of the control animals, however, was made up to a greater extent of fibrous tissue, noncalcified cartilage and osteoid tissue, and contained approximately from 20 to 35 per cent less calcified cartilage and spongious bone tissue than that of the treated cats. Moreover, the spongious bony framework of the endosteal callus was denser in

the latter than in the control animals. A union of the spongiosa proliferating from the ends of the fragments was present in many places in the fractures of the animals that received injections, while this condition was only rarely seen in the fracture line of the control animals, in which a fibrous tissue mixed with calcified or noncalcified cartilage tissue separated the endosteal spongiosa of the fragments.

COMMENT

Calcium and phosphorus are looked on as stimulants to the growth of osteoid tissue. The observed increase in the amount of callus formation may therefore be interpreted as the natural response of the periosteum and endosteum to the augmentation of the phosporus and calcium in the blood produced by the administration of the parathyroid extract. The hastening of the calcification of the callus can also be explained by the chemical changes in the blood. Emmet Holt [8] states that "the tertiary calcium phosphate is precipitated with moderate rapidity when the ion product is greatly in excess of the solubility product constant, precipitation proceeds with great slowness when the ion product is only slightly in the excess of the value of the constant. The rate of precipitation depends on how much the value of the solubility product constant is exceeded." From my observations, the parathyroid extract may be found to be of therapeutic value in cases in which the calcification and production of osteoid tissue is delayed, as for instance in the nonunion of fractures, in which, according to Tisdall and Harris,[9] the rise of the blood phosphorus which normally takes place after a fracture is found insufficient or delayed. The administration of parathyroid extract may possibly produce favorable effects in rickets, at present most successfully treated with the quartz lamp, which causes also an increase of the calcium and the phosphorous of the blood. Reports of the successful treatment of ostitis fibrosa with the implantation of parathyroid tissue (Mandl [10]) or the administration of parathyroid tablets (Bassler [11]) are already found in the literature and substantiate my observations and suggestions.

The therapeutic use of the parathyroid extract presents certain dangers for the patient which must be kept in mind. In a previous paper, I reported the disastrous effect of acute parathyroid poisoning which was produced by single or accumulated overdoses of parathyroid extract. But even the administration of this substance in proper intervals and

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8. Holt: Studies in Calcification, J. Biol. Chem. **64**:567, 1925.

9. Tisdall, F. F., and Harris, R. I.: Calcium and Phosphorus Metabolism in Patients with Fractures, J. A. M. A. **79**:884 (Sept. 9) 1922.

10. Mandl: Therapeutischer ersuch bei Ostitis fibrosa generalisata, Klin. Wchnschr. **5**:438, 1926.

11. Bassler, A.: An Interesting Result from the Use of Parathyroid Extract in a Case of Osteitis Deformans (Paget's Disease), J. A. M. A. **87**:96 (July 10) 1926.

in amounts which do not cause any serious clinical symptoms may result in pathologic alterations in vitally important organs, such as the myocardium and the suprarenal gland, as was shown in the experiments. Its use, therefore, is not advisable in patients with circulatory weakness, a conclusion which is emphasized from a physiologic point of view by Edwards and Page.[12]

CONCLUSIONS

1. Repeated injections of parathyroid extract apparently stimulate the production and calcification of osteoid tissue.

2. Necroses seen in the myocardium and in the cortex of the suprarenal gland after the repeated administration of parathyroid extract point to the dangers connected with its therapeutic use.

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12. Edwards and Page: Effects of Parathyroid Extract on Heart and Circulation, Am. J. Physiol. **78**:235, 1926.

Laboratory and Technical Notes

THE USE OF CALCIUM CHLORIDE IN THE FORMATION OF EXPERIMENTAL STAPHYLOCOCCUS ABSCESSES*

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The experimental production of skin abscesses by laboratory cultures of staphylococci is a useful means of investigating problems of resistance. To be available for this purpose, it is necessary that the results should be uniformly positive in normal animals. Rubbing the cultures on the dorsal skin of rabbits proved unsuccessful, even when the skin was scarified, or bruised by pinching with hemostatic forceps. Hypodermic and intradermic injection of suspensions of agar slant cultures in physiologic sodium chloride solution also proved unreliable: of nine injected animals, only one developed an abscess, and this only after eight days; large doses sometimes killed the rabbits without producing an abscess. The results were not improved by bruising the skin or by causing local ischemia by an intradermal injection of epinephrine hydrochloride.

Successful results were finally secured by suspending a twenty-four hour agar slant culture in a 1:500 solution of calcium chloride, in the volume of 2.5 cc. per kilogram of body weight. In each of seven cases in which injection was performed in this manner, the rabbits developed a definite abscess within twenty-four hours. Weaker solutions of calcium chloride, 1:750 and 1:1,000 were unsuccessful, although the volume was increased so that the same quantity of the salt was injected. Stronger solutions, 1:250, produced local necrosis even without the cultures, while the control injections of uninfected 1:500 solutions caused no lesions.

The suggestion for this use of calcium chloride for lowering local resistance to infection was furnished by Bullock and Cramer's[1] work on "kataphylaxis," and the studies on silica by Gye and Kettle,[2] and Cummins.[3] I am inclined to consider the action of the calcium as nonspecific, i. e., as due simply to the toxic, subnecrotic action of the calcium salt on the tissue. Further experiments in this direction are in progress.

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1. Bullock and Cramer: Roy. Soc. London **90**:515, 1917.

2. Gye and Kettle: Brit. J. Exper. Path. **3**:241, 1922.

3. Cummins: Brit. J. Exper. Path. **3**:237, 1922.

General Review

PATHOGENICITY OF HUMAN INTESTINAL PROTOZOA *

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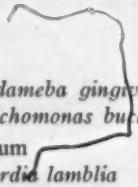
The stimulus given by the late war to the study of the intestinal protozoa of man has resulted in great advances during the past ten years in the knowledge of this group of human parasites. But, of the hundreds of "species" described and named by men in various parts of the world, only a few have withstood the careful investigations of protozoologists. At present fifteen well established species are recognized, and each of the four large classes of *Protozoa* is represented by one or more species. In *Sarcodina* are *Endameba histolytica, E. coli, E. gingivalis, Endolimax nana, Iodameba williamsi* and *Dientameba fragilis;* the *Mastigophora* include *Trichomonas hominas, T. vaginalis, T. buccalis, Chilomastix mesnili, Giardia lamblia, Embadomonas intestinalis* and *Tricercomonas intestinalis; Sporozoa* has only one representative, *Isospora hominis,* and *Infusoria* also only one, *Balantidium coli.* Each species is located in a more or less definite section of the digestive tract as follows:



Mouth
- *Endameba gingivalis*
- *Trichomonas buccalis*

Duodenum
- *Giardia lamblia*

Small Intestine
- *Isospora hominis*

Large Intestine
- *Endameba histolytica*
- *Endameba coli*
- *Endolimax nana*
- *Iodameba williamsi*
- *Dientameba fragilis*
- *Trichomonas hominis*
- *Chilomastix mesnili*
- *Embadomonas intestinalis*
- *Tricercomonas intestinalis*
- *Balantidium coli*

Vagina or Urinary Tract
- *Trichomonas vaginalis*

The species that occur in the mouth, vagina and urinary tract are, of course, not "intestinal" protozoa, strictly speaking, but for convenience they are usually included in this category.

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Only three of the species listed have been positively proved to be pathogenic; these are *Endameba histolytica, Isospora hominis and Balantidium coli.* Most of the others are under suspicion, but efforts to incriminate them beyond all doubt have been found extremely difficult. Even those that are known to be pathogenic may not always bring about changes in the body of the host, or, if they do always harm the host the injuries they inflict are frequently too slight to bring about the appearance of symptoms. In the following pages an attempt is made to present some of the more recent investigations that concern the pathogenicity of these organisms. It has not been possible to include all of the numerous contributions to this subject but I have tried to set forth the present status of the problem with fairness to all.

INTESTINAL AMEBAS

Only three of the six well established species of amebas that live in man have been considered pathogenic. The harmless species are *Endolimax nana, Iodameba williamsi* and *Dientameba fragilis.* Of the other three, *Endameba histolytica* is recognized by every one as pathogenic to man, whereas *Endameba coli* and *Endameba gingivalis* are still of doubtful pathogenicity.

Endameba gingivalis.—Endameba gingivalis lives in various places in the mouth, but especially in the tartar of the teeth and in the materia alba around them; the finding of this organism has been reported in many suppurative and inflamed conditions of the mouth and throat. That this species does not require access to the tissues is indicated by the fact that Lynch (1915) found them in the crevices between the false teeth of persons with healthy gums. Various new species have been described from abscesses in the jaws and tonsils, but these were probably all somewhat modified *E. gingivalis.* The presence of large numbers of these amebas in the lesions of pyorrhea alveolaris led Smith and Barrett (1915) and Bass and Johns (1915) to conclude that they are responsible for this disease, and on their recommendation emetine was widely used in its treatment. More recent studies indicate that the species is harmless. Its food consists principally of leukocytes and a few bacteria (Kofoid and Swezy, 1924). Smith and Barrett (1915) record the ingestion of red cells, and Howitt (1926) finds that washed red cells of the guinea-pig are eaten by specimens in artificial cultures, but erythrocytes are probably seldom devoured in nature.

Endameba coli.—Endameba coli appears to be present in about 50 per cent of all human beings. It lives in the large intestine only and is usually considered nonpathogenic. Its food consists of bacteria, yeast, starch grains, other protozoa and all sorts of débris contained in

the large intestine. It differs markedly from *E. histolytica* in its failure to ingest red blood cells. Lynch (1924) has reported a case in which an ameba that formed an eight-nucleated cyst which was indistinguishable from cysts of *E. coli* ingested red cells. Fecal material was inoculated into a medium of salt solution to which a small amount of human blood had been added and placed in a "warm incubator." Two hours later the majority of the amebas from the bottom of the tube had ingested red cells. Amebas from the same patient at a later date failed to ingest red cells.

There is some evidence that under certain conditions *E. coli* may invade the tissues of the intestinal wall. Brumpt (1926) has compiled the scattered data available from reports on human beings, and has added facts obtained by himself from experiments on kittens. Brumpt found specimens of *E. coli* in small ulcerations in the intestinal mucosa of a kitten that had been given a rectal injection of material containing both *E. coli* and *E. dispar,* the latter being the name given by him to what he believes to be a species resembling *E. histolytica* morphologically, but differing from it in being nonpathogenic. If this work and the observations of Lynch are confirmed, it must be admitted that under certain conditions *E. coli* may eat red blood cells and invade the tissues of the intestine.

Endameba histolytica.—The large number of surveys made during the past ten years indicates that on the average about 10 per cent of the general population are infected with this species. The primary site of infection is the large intestine, and amebic ulcers are most often located in the dependent portions where the greatest stasis exists, namely, the cecum, ascending colon, rectum, sigmoid and appendix. In a resumé of 6,800 postmortem examinations made in the Panama Canal Zone from 1905 to 1923, principally by Darling and Clark, the latter (Clark, 1924) states that 186 persons died of amebiasis or had amebic ulcers in their intestines (27 cases). The ulcers were scattered throughout the colon in 113 cases (60.7 per cent), but in 63 cases (33.8 per cent) they were limited to the dependent regions mentioned.

An interesting point regarding the activities of the amebas in primary amebiasis has been raised by the recent discovery that when grown in cultures (Boeck and Drbohlav, 1925) *E. histolytica* will ingest bacteria and thrive without access to the intestinal wall. Before these facts were established, it was supposed that this species required tissue elements for food, and hence was always pathogenic, whereas it now seems probable that in some cases the organisms are able to grow and multiply in the lumen of the intestine, and may hence be as harmless in certain carriers as are *Endameba coli* and the other nonpathogenic species listed.

The liver is recognized as the principal secondary site of infection. Amebas are supposed to reach the liver by way of the blood stream, which they invade through the capillaries in the intestinal wall. Patients with intestinal amebiasis are at some time liable to develop abscesses of the liver. Cases that are brought to autopsy usually reveal a high percentage; for example, Clark (1924) records 51 per cent of abscesses of the liver among 186 deaths in the Panama Canal Zone due to amebiasis.

Why amebic infections are not frequently set up in the ileum or do not spread into the ileum from the large intestine is still unexplained. Rarely, amebic ulcers have been reported from the small intestine. Allen (1924), for example, in one case found the lower two feet of the ileum infected, the ulcers being small and superficial. Amebas were found in the submucosa, mucosa and circular muscles. The large intestine of this patient was severely ulcerated. Craig (1926) states that he has "observed several cases in which typical amoebic ulcerations containing the amoebae were present in the lower portion of the ileum in the region just above the ileocaecal valve." Sellards and Theiler (1924), working with cats, found that in several of the older animals with histolytic infections of several weeks' duration the amebas spread into the small intestine above the ileocolic sphincter. They found that by ligating the large intestine and forcing water into the digestive tract with a stomach tube they were able to cause the distention of the ileocolic sphincter. In three kittens thus treated the amebas infected the lower part of the small intestine. This result suggests that the sphincter ordinarily mechanically prevents the passage of the amebas into the ileum. In three other kittens no infection was obtained when the ileum was lighted and trophozoites were injected above the ligature.

A number of other secondary sites of infection with *E. histolytica* have been noted besides the liver and ileum; many of these have been in parts of the body at a considerable distance from the large intestine and can be explained only on the assumption that amebas are carried there in the blood or lymph. When an amebic ulcer is formed in the wall of the large intestine, blood vessels are opened, thus giving amebas access to the blood stream; specimens have actually been observed in the capillaries of the intestinal wall. Such amebas may obviously be carried to any part of the body and may initiate infections wherever suitable conditions are encountered.

Abscesses of amebic origin may occur in the lung, brain, spleen or other organs. Pulmonary abscesses may be due to rupture of an abscess of the liver or to amebas carried to the lungs in the circulation. The lower lobe of the right lung is the most common location. Abcesses in the lung may rupture into the air passages, and the pus,

containing amebas, may be coughed up by the patient. Amebas carried into the brain may give rise to cerebral abscesses, of which about fifty have been recorded, all ending fatally. Several cases of splenic abscess have been reported. Amebas have also been reported from the urinary tract, the testis, the skin, the eye, the bone marrow and the lymph glands. Whether the "organisms" described in all of these cases were amebas of the species *histolytica,* and whether they were responsible for the various diseased conditions ascribed to them are still unsolved questions.

One of the most interesting phases of amebiasis that has stimulated discussion of recent years is that of host-parasite relations during the carrier period. There are three principal points of view with regard to this. This first is that the amebas live as harmless commensals in the lumen of the intestine. This was considered impossible until recent cultivation experiments proved that tissue elements are not necessary for the growth and reproduction of the trophozoites.

The second view is that the amebas require access to the tissues of the intestinal wall; that they must have tissue elements for their growth and reproduction, and that they therefore always injure the body of the host. These injuries, however, because of resistance of the host, are so slight that they are repaired by the regeneration of tissue as rapidly as they are incurred, the result being a sort of equilibrium between host and parasite.

The third view is that a large proportion of carriers suffer from "chronic" amebiasis. Kofoid and his colleagues have been studying this phase of the subject for several years. They state:

> It has been possible for the last two years to say that there is a definite disease entity that can be recognized by clinical means as chronic amebiasis. According to our own records, this is so definite that fully 95 per cent of cases can be diagnosed clinically before laboratory confirmation is obtained. . . . Over a period of years, constant search has been made for a true carrier, but as yet only one individual has been found by the medical author in more than 500 cases who showed no visible tissue damage attributable to *E. dysenteriae* [= *E. histolytica*]. . . . In symptomatology, one of the salient facts is that persons with amebiasis commonly complain of fatigability. They go to bed tired, and arise in the morning tired; they are tired whether they work or rest; many of them are so tired that they are in actual anguish; others merely say they have lost their "pep." Very commonly associated with fatigability is constipation, or constipation interspersed with evanescent diarrheas. Occasionally one will elicit the passing of considerable quantities of mucus or blood. A normal man knows hunger and the desire for evacuation; otherwise his bowel does not obstrude on his consciousness. In amebiasis the patient often has no actual pain. On the other hand, he is not comfortable in the abdominal region. He is, as we say "bowel conscious." He may have considerable flatulence. He may or may not complain of definite soreness in the right lower quadrant, in the right upper quadrant, or in the region of the splenic flexure. He may complain of neuritic symptoms, pain along the course of some particular nerve or nerves. He may complain of basal headache, or of pain

and aching in the region of joints. He may have considerable digestive disturbance, referable to the upper abdomen, that leads to the clinical suspicion of hyper-acidity, hypo-acidity, gastric and duodenal ulcers, chronic pancreatitis, chronic cholecystitis, chronic duodenitis or chronic hepatitis. He may complain of cough and expectoration, with blood sputum. He may complain of rapid pulse, and one may see mild tachycardias. He may complain of much nervousness, and one may find in him symptoms of a subacute or chronic thyroiditis. He may complain of defective vision, and one may find greatly impaired vision with or without definite iritis. Some may complain of disabling loss of memory, while others show various neuroses. One may find also the grosser lesions of liver abscess, lung abscess, brain abscess, skin ulcers, etc. The matter can be summed up by saying that in chronic amebiasis we are dealing with a disease entity as protean as syphilis." (Boyers, Kofoid and Swezy, 1925.)

Acton and Knowles (1924) are also among those who believe the "healthy" carrier is not always free from clinical symptoms. They "recognize two well marked types of *E. histolytica* carriers; the first, the thin, lean, cadaverous individual whose food assimilation is inadequate, who tends to be faddy and irritable, who is vaguely ill, without knowing what is wrong with him; the second the fat jovial type, with good food assimilation, a bon viveur, who soon discovers, however, that indulgence in 'short drinks' at the club bar is apt to be followed by trouble. Together with minor ulceration of the colon mucosa by the entamoebae goes a train of ill-defined symptoms," which they describe in detail under the subheads; irregularity in the state of the bowels, pain, fever, bacterial embolism and absorption of poisonous pressor bases from the ulcerated intestine.

Craig (1927) states that his experience indicates that more than 50 per cent of the so-called carriers of *E. histolytica* present some symptoms apparently caused by the presence of these amebas in the intestine. These symptoms are largely confined to the digestive and nervous systems. Constipation and diarrhea are perhaps the most common; lack of appetite is frequent and is associated with loss of weight, and evanescent neuralgic pains in the lower portion of the abdomen and other symptoms are characteristic. The symptoms referable to the nervous system are of the neurasthenic type. A mild degree of anemia and occasional subnormal temperature may occur. Craig advises the routine examinations of stools and efforts to cure carriers.

Kofoid (1923) believes that arthritis deformans of Ely's second type is the result of infection with *Endameba histolytica*. He has found amebiasis in a number of cases of this disease and gives the prevalence of chronic rheumatism of the joints in the tropics, where amebic dysentery is common, as confirmatory evidence. Cells resembling *Endameba histolytica* were discovered by him and his colleagues in the ends of the diseased bones in the region around the necrotic areas. Kofoid beleves that these were *E. histolytica*, because during

mitosis the nuclear membrane remained intact, an intradesmose was formed and six chromosomes were present. He says:

> We conclude, therefore, that arthritis deformans of the second type is accompanied by amebic infection of the bone marrow and that this infection is found in the immediate neighborhood of the bone lesions where the tissues have been destroyed. . . . It is a matter of importance that the presence of the amebae in bone stimulates it to abnormal growth just as their presence in the bowel leads to the thickening of the wall by the abnormal multiplication of its cellular elements.

Kofoid (1923) also believes that there is a connection between amebiasis and Hodgkin's disease. He reports two cases; both patients were carriers of *E. histolytica,* and in their diseased lymph glands were found cells resembling this protozoon and presenting in mitosis the various characteristics noted. The evidence at present available appears to be insufficient to establish *E. histolytica* as the etiologic agent of arthritis deformans and Hodgkin's disease, but if such a relationship exists, it should be possible to prove it by further study.

A problem of considerable interest to pathologists is the prevalence of clinical amebiasis in the tropics and its virtual absence in the temperate zones, although the causative agent is present in about 10 per cent of the inhabitants of the latter. No satisfactory explanation of this situation has been established. The three principal suggestions that have been offered are climate, lack of sanitation and differences in the virulence of the parasite or resistance of the host. Brug (1925) is an exponent of the climate theory and sets forth considerable evidence that dysentery is most prevalent during the warmer part of the year, but does not explain how differences in temperature bring about this result. The second theory mentioned involves the frequent ingestion of large numbers of organisms because of lack of proper sanitation. According to the third suggestion, either the amebas of the tropics are more virulent, or tropical conditions lower the resistance of the hosts to such an extent that extensive invasion of the tissues results. I am inclined to favor the last mentioned theory, but it still remains to be proved.

INTESTINAL FLAGELLATES

For many years it was customary among physicians to refer to intestinal flagellates as cercomonads or "ciliated monads." As a matter of fact, no species of the genus *Cercomonas* is known to be a human parasite, and ciliated monads do not exist. The species to which these names were applied are no doubt *Trichomonas hominis* and *Chilomastix mesnili.* The latter was distinguished specifically from the former in 1910. Two new and distinct species of intestinal flagellates were described by Wenyon and O'Connor in 1917 as *Embadomonas intestinalis* and *Tricercomonas intestinalis.* These species appear to be rare and nonpathogenic, and hence of no practical importance.

Giardia lamblia.—The terms lambliasis, giardiasis and flagellate diarrhea all refer to a pathologic condition supposed to be due to the presence of *Giardia lamblia*. Most of the infected hosts do not exhibit any symptoms; they are carriers. A few persons, however, are afflicted with a diarrheic condition that is persistent; the presence of large numbers of giardias in their stools and the absence of any other organisms that are known to be the etiologic agents of diarrhea indicate, but do not prove, that the giardias are responsible. Diarrhea is known to result from the irritation of the epithelial cells of the intestinal wall, and no doubt such irritation is brought about when vast numbers of giardias are moving about in the duodenum and attaching themselves by means of their sucking disks to the surface of the cells. When few in number, the symptoms produced in this mechanical way would be so slight as to pass unnoticed, but millions of specimens present at one time might aggravate conditions and bring about diarrhea. Giardias in large numbers might also be injurious to the host as a result of the excretion of waste products or possibly of some specific toxic substance, and might even interfere with digestion and absorption due to interference with the glands and epithelial cells as Haughwout (1918) has suggested.

It is generally recognized that the young of both man and lower animals are more susceptible to infection and more frequently infected with *Protozoa* than are adults. Thus it has become the custom to select young animals for laboratory experiments. In the case of *Giardia lamblia* considerable information exists on this subject. Dobell (1921) has collected the following data.

Occurrence of Giardia Lamblia

Investigator	Place	Per Cent of G. lamblia	
		Adults	Children
Mathews and Smith	Liverpool	7.0	14.1
Campbell	Bristol	3.9	16.3
Miss Nutt	Leeds	3.8	39.8
Miss Nutt	Sheffield	7.2	15.8
McLean	Reading	9.3	17.4

Similar results have been obtained by Maxcy (1921) in the United States and by Simon (1924) in Germany. Maxcy found 17 per cent of infection in children, aged from 1 to 5 years, but almost 40 per cent in children, aged from 6 to 12 years. Simon (1924) found 23.4 per cent of infection in a group of 137 persons; 77.4 per cent of these, who were under 15 years of age, gave an incidence of 27.4 per cent. His youngest patient was a child, aged 9 months; Miss Nutt records infections in children, aged 3 weeks, 3 months, 9 months, 11 months and

12 months. Dobell suggests that the higher incidence among children may be due to the greater ease of finding the organisms in their stools. It seems more probable that some type of host resistance develops with age. Excystation may be impossible, or the escaping trophozoites may find the intestinal contents of adults less favorable than those of children for their growth and reproduction. Miller (1926) describes the stools of children suffering from giardiasis as characteristic of chronic enterocolitis, containing much undigested food and mucus and being perhaps slightly acid.

Those who claim that giardias are pathogenic base their belief partly on the fact that the flagellates disappear when symptoms cease. This evidence cannot be accepted at its face value, however, since giardias are usually common only when the stools are loose, a fact recognized by Leeuwenhoek in 1681. As soon as the stools become formed, trophozoites are no longer passed, and cysts may or may not be present. Trophozoites can generally be obtained from infected persons, however, with the aid of a purge. Crucial experiments are therefore still necessary to prove that the giardias are the cause of the diarrhea and not simply mechanically brought down when this condition exists.

The primary site of infection with giardias appears to be the duodenum. In rats the trophozoites of *Giardia muris* were more than twice as numerous in the duodenum as in the jejunum and almost entirely absent from the ileum (Hegner, 1923).

The bile ducts and gallbladder appear to be secondary sites of infection for *Giardia lamblia*. Many reports of infections in these organs have appeared in the literature during recent years, but these reports are confusing, and it is difficult at present to arrive at definite conclusions. Boyd (1921) and Silverman (1923) reported cases in which the microscopic examination of the liquid obtained by duodenal tubage revealed numerous trophozoites of *Giardia;* this was soon followed by a description of three similar cases by Libert and Lavier (1923). In the same year Westphal and Georgi (1923) also found *Giardia* in the duodenal fluid of a patient suffering from cholecystitic symptoms. On removal of the gallbladder, large numbers of giardias were found in this organ. Less convincing evidence is that of Felsenreich and Satke (1923), who maintain that various disturbances of the liver and gallbladder are due to giardias that occurred in large numbers in duodenal juice. Similar evidence is offered by Labbé, Nepveux and Gavrila (1925) and Pappalardo (1925) to explain symptoms of what they designate "vesicular lambliasis." On the other hand, Chiray and Lebon (1925) report a case of cholecystitis in which giardias were abundant in the duodenal juice, but absent from the excised gallbladder, and Gaivoronsky (1925) described two similar cases, one of cholecystitis and the other of gall-

stone. The data available indicate that giardias may migrate through the bile ducts and into the gallbladder, but do not prove that they are responsible for the disturbances associated with their presence.

Trichomonas buccalis.—Trichomonads occur in the mouth, intestine, vagina and urinary tract. Certain morphologic differences exist among these that are considered by some to be sufficient to place them in different genera. Thus, the type species, *Trichomonas vaginalis,* has four anterior flagella, and the genus *Trichomonas* is therefore characterized by the presence of this number of flagella. Certain intestinal forms have four flagella, but others have been described with three and five. The generic terms *Tritrichomonas* and *Pentatrichomonas* have been coined for the latter. The situation as regards the pathogenicity of the trichomonads is much the same as that indicated in the discussion of *Giardia;* that is, the flagellates are often particularly abundant in disease conditions, but have not been incriminated with certainty.

Recent investigations indicate a definite relation between the presence of *T. buccalis* and disease of the oral region. Thus Hogue (1926) found that all of her positive cases gave a history of pyorrhea, acute gingivitis or abscessed teeth, and Hinshaw (1926) found no specimens in normal mouths, but records thirty-seven positive cases from forty-nine patients with advanced pyorrhea and no positive cases from seventy-one persons with normal mouths or with incipient pyorrhea. This flagellate seems, therefore, to be associated with pathologic conditions, but it is yet to be proved responsible for pyorrhea.

Trichomonas vaginalis.—This species seems to be more widely distributed and more frequent in women than generally supposed. Brumpt (1913) found it in over 10 per cent of the women examined at a gynecologic clinic in Paris; Barlow (1916), in 5 per cent of 100 women at a similar clinic in St. Louis; Reuling (1921), in 18.4 per cent of 250 women in a clinic in Heidelberg; Ponoschina (1923), in 30 per cent of 55 women, but not in 22 girls aged from 2 to 14, and Hegner (1925), in 50 per cent of 32 women in Honduras and Costa Rica. Recent reports of trichomonads in the urinary tract of men have been furnished by Katsunuma (1924) and Dastidar (1925). Katsunuma describes *T. vaginalis* in the urine of a Japanese boy only 3 years old. No trichomonads were present in the feces, and the urinary tract was apparently normal. The flagellates were thought to be located in the terminal portion of the ureter, and the boy was thought to have been infected by his mother or some other woman attendant. Dastidar (1925), during the routine examination of fresh urine from about 1,000 persons, found trichmonads in that of three men and one woman. In all four cases the urine was acid, and that of the three men contained pus cells; in two

of the latter, the flagellates and pus cells disappeared at the same time, which indicates that some relation may exist between the trichomonads and pathologic condition.

The relations of *T. vaginalis* to its host cannot be stated with certainty. It is reported to be present commonly when the vaginal mucous membrane is in an abnormal condition and when the reaction of the vaginal mucus is acid. Treatment with sodium bicarbonate is therefore recommended by some physicians, so as to change the vaginal contents to an alkaline condition. Whether the trichomonads are pathogenic and bring about a disease condition in the vagina, or this condition is favorable for the growth and multiplication of the flagellates, is a question not yet solved.

Trichomonas hominis.—Intestinal trichomonads have been reported with three, four and five anterior flagella. These flagellates are often accused of causing diarrhea or trichomoniasis. The form with five flagella, known as *Pentatrichomonas ardindelteili,* seems to be particularly pathogenic. Pentatrichomonads have more often been found associated with diarrheic conditions than the other types and have frequently been reported to have ingested red blood cells. Derrieu and Raynaud (1914) first reported this type in cases of dysentery in Algiers; Chatterjee (1915, 1917) found it in thirty cases of chronic dysentery in Bengal; Wenyon and O'Connor (1917) cite one case in the Near East; Haughwout and de Leon (1919) found it in a case of acute dysentery in Manila; and Kofoid and Swezy (1924) describe it in three patients with histories of chronic diarrhea, all of whom had lived in the tropics or had come into close contact with persons who had. Up to that time, this five-flagellated type had been found only in hosts who had diarrhea or dysentery. The presence of an organism under conditions of pathogenicity and the ingestion of red blood cells by it is not enough to prove that it is pathogenic. The diarrheic or pathogenic condition may have rendered the intestinal contents particularly favorable for the growth and reproduction of the flagellate, and the presence of the red blood cells in the intestinal contents may have offered the flagellates an opportunity to take them in with other kinds of food particles and does not prove that the flagellates actually attack the tissues of the host. Furthermore, cases of infection with *Pentatrichomonas* have been reported (Hegner, 1925) in which the patients have never exhibited any signs of diarrhea or dysentery. Kessel (1925) has reported the ingestion of red blood cells by the four-flagellated trichomonad, *Trichomonas hominis,* found in the stool of a patient suffering from bacillary dysentery, and in *Trichomonas hominis* (*vaginalis?*) from the urine of another patient passed at the time of menstruation; Reichenow (1925) finds that in culture both the four-flagellated and five-flagellated types will ingest red blood cells, and Wenyon (1926) states that he has observed them in

specimens passed by a patient suffering from bacillary dysentery and in cultures containing rabbit blood. It seems probable that under certain conditions all types of trichomonads may take in erythrocytes.

There has been considerable discussion regarding the tissue-invading powers of trichomonads (Haughwout, 1918; Hadley, 1919), but little actual data are available. Wenyon (1920) made a histologic study of the intestinal wall of five patients who had died of pneumonia and were infected with trichomonas. "There were no noticeable lesions of the intestine which one could attribute to the flagellates." Not only were the flagellates distributed over the surface of the mucosa, but they were also found in the lumen of the glands of Lieberkühn, in some cases in large numbers. Definite ruptures of the glandular epithelium were noted in one case, and the trichomonads "were evidently passing through these." The "flagellates were scattered about in the interglandular loose connective tissue, so that there was a definite invasion of the tissues of the gut. . . . There never appeared to be an extension of the invasion beyond the mucous layer. Furthermore, there did not seem to be any reaction on the part of the tissue as regards cell proliferation or invasion." If an organism that injures the tissues of its host is considered pathogenic, then *Trichomonas hominis* may be pathogenic in certain cases; but it is not known how often it invades the tissues nor whether this invasion is sufficient to bring about the condition known as flagellate diarrhea.

Intestinal trichomonads are not known to set up infections in any part of the body other than the large intestine. Flagellates of this group have been reported from the blood of pigeons, snakes, rats and mice, but mostly at autopsy. Pentimalli (1923) claims to have found trichomonads in the blood of a man, and Kessel (1925) found *T. hominis* in the pus of an amebic liver abscess; he believes that it reached this location by way of the blood stream from the intestine, but had no evidence on this point except the presence of the organism in the liver, at a distance from its normal habitat.

Chilomastix mesnili.—Chilomastix mesnili, which is found in the large intestine, has been reported in about 3 per cent of the thousands of persons examined by various investigators. It has been considered the cause of flagellate diarrhea, but certainly on insufficient evidence. Proof of its pathogenicity, therefore, is still to be furnished.

INTESTINAL COCCIDIA

Coccidia has been described from both the liver and small intestine of man, but it seems to be rare in the human host. Almost all of the approximately 200 cases of human coccidiosis now on record have been reported since 1915, and are referable to one species, namely, *Isospora hominis.* The species *Eimeria wenyoni, E. oxyspora* and *E. snijdersi*

named by Dobell (1919, 1920) as parasites of man, have since been demonstrated by Thomson and Robertson (1922, 1926, 1926) to be *E. sardinae,* which occurs in the testes of sprats and herrings, and *E. clupearum,* which inhabits the livers of herrings, sprats and mackerel. The oocysts of these species were ingested with infected food and were later found in the feces of the human host who had eaten them; they had simply passed through the digestive tract without being destroyed.

Practically nothing is known regarding the life cycle of *Isospora hominis* within the body of man, but lower animals are frequently infected with species similar to the human parasite, especially cats and dogs, which are the hosts of *Isospora felis* and *I. rivolta.* Some idea may be obtained, therefore, of the character of the attack on the human host by studies of these species in cats and dogs. In the first place, infection always involves the penetration of the epithelial cells of the small intestine by sporozoites, and later, as a result of asexual reproduction, by merozoites. As a result of this invasion a large part of the intestinal epithelium may be eroded. Thus the organism is always pathogenic in animals, and probably also in man.

Infections involving the production of symptoms can be brought about in cats by feeding them as few as 100 oocysts, but the larger the number used the more severe the infection. For example, Andrews (1927) found that doses of from 100 to 60,000 oocysts led to the appearance of symptoms, but the animals recovered, whereas inoculations with 100,000 oocysts resulted in death. A remarkable feature of infection with *Coccidia* is the greater length of the prepatent period [1] as compared with the incubation period. Thus Andrews (1927) reports the prepatent period of *Isospora felis* in seven cats as five or six days, whereas the incubation period was only two to four days in the same animals.

The best account of a case of human coccidiosis is that reported by Connal (1922). According to Connal, fecal material containing oocysts of *Isospora hominis* was accidentally thrown over the face of a laboratory worker, aged 40. Some of the oocysts were probably swallowed. After an incubation period of six days, the patient suffered from diarrhea, during which the feces appeared similar to those passed after a saline purge; this continued for twenty-two days, and then the feces became more copious and of a thick, oily consistency. Seven days later the stools became less fluid, and during the next two days became formed. Oocysts appeared in the feces twenty-two days after diarrhea commenced, giving a prepatent period of twenty-eight days. The patent period continued for thirteen days, i. e., during the second diarrheic

1. By the prepatent period is meant the length of time from inoculation of the parasite until it can be recovered from the host by a designated technical method.

period and for four days after the feces became formed. No oocysts were observed in the feces during the succeeding six months, and diarrhea did not occur again. Evidently no relapse has been suffered by the patient, since an account of it has not been reported.

Other cases of coccidiosis in man have recently been reported that add to the evidence of the disease-producing powers of *Isospora hominis*. Thus Pons (1925) has described two cases. The first patient suffered with a choleric syndrome for six days; he subsequently appeared normal for ten days; diarrhea, with stools containing blood and mucus, then commenced and continued for nine days; a normal period of twenty days ensued; diarrhea again appeared, lasting six days. Giardias were noted, but no dystentery bacilli or other pathogenic organisms. Oocysts appeared three days before the end of the last diarrheic period, and did not definitely disappear until thirty days later. The second case reported by Pons was that of a woman who had suffered from attacks of diarrhea for ten months before *Coccidia* was discovered in her feces. Oocysts were passed for sixteen days, and then no more could be found.

In several respects these two cases resemble that of Connal, and infections in cats and dogs: 1. Diarrhea preceded the appearance of the oocysts, that is, the incubation period was shorter than the prepatent period. 2. The oocysts appeared for several weeks, and then were apparently entirely eliminated, the patent period being thirteen days in Connal's case, thirty and sixteen days respectively in Pon's cases, and thirty days in cats and dogs. 3. Relapses were not reported. The literature contains descriptions of a number of other cases of human coccidiosis; for example, Haughwout (1921) reports a case in an American in the Philippines who was suffering from occasional watery diarrhea; Boon van Ostade (1923) reports a case in a Malay who had acquired the disease in Java or Sumatra and who had chronic diarrhea; Petzetakis (1925) reports it in a patient with acute dysentery, and Leger (1926) also reports a dysenteric case, in Annam.

INTESTINAL CILIATES

A number of ciliates have been described from the intestine of man, but only one species, *Balantidium coli*, can be recognized as authentic. There appears to be no question regarding the pathogenicity of this species, but only on rare occasions is balantidiosis frequent enough to furnish an adequate idea of its incidence. For example, Aguilar (1925) states that, during the period from August 30 to October 2, 10 per cent of the patients admitted to the hospital in Quirigua, Guatemala, were infected with *Bal. coli*. Whether the ciliates are able to live and reproduce in the lumen of the intestine without access to the tissues of the host is not known. It is generally believed that the intestinal epithelium

is always invaded and that when no symptoms are observed the parasite is living in equilibrium with its host; that is, tissues are regenerated as rapidly as they are broken down. Aguilar's observations indicate that perhaps all infected hosts exhibit symptoms, since every one of the forty patients recorded by him gave a history of diarrhea, and fourteen of them were passing pus or pus and blood in their stools.

Invasion of tissues occurs only in the large intestine. No additions to the knowledge of the method of penetrating the tissues have been made since Walker (1913) described the migration of the organisms into the mucosa by mechanically boring their way between the crypts. They are to be found in the mucosa, submucosa, muscular layer, blood and lymph vessels and lymphatic glands, where they are supposed to secrete ferments that dissolve the surrounding cells and thus produce ulcers. Campos (1924) found many specimens in the blood vessels of the intestinal wall and in the lymphatic glands of that region, but none could be recovered from other organs, such as the lungs, stomach, duodenum, liver, kidney, pancreas and brain, and hence it seems probable that specimens that make their way into the circulation are unable to set up an infection in any part of the body. According to Danisch (1924), *Bal. coli* is pathogenic only when the contents of the large intestine, which are normally acid, become alkaline.

Evidence continues to accumulate that *Bal. coli* from the pig, man and other primates belong to one species, and that man obtains his infection from the pig. For example, Young and Walker (1918) report a patient who worked in a packing house as a gut-stripper, and frequently got fecal material in his mouth; De Buys (1918) reports a case in a colored boy, aged 5, who "had been accustomed to help 'round up' the pigs in the pen every day and frequently would eat some food which he would hold in his hand while helping with the pigs. It was his habit also to go into the pen at times when he ate his food." Cordes (1921) describes a case in a pork butcher who had been slaughtering pigs for thirty years; Graziader and Mario (1922) had a case in a peasant who was accustomed to eat raw salad grown in soil fertilized with pig manure; and Jausion and Dekester (1923) report two cases from Morocco in villagers who were closely associated with pigs.

There is also evidence that, although *Bal. coli* appears to be a "natural" and harmless parasite of the pig, it may at times become pathogenic to this animal. Brumpt (1909) describes a pathogenic infection of a young pig with balantidia from monkeys; Haughwout (1918) also reports lesions due to *Bal. coli* in the pig; and Ohi (1923-1925) claims that this protozoon is pathogenic to pigs in Southern Formosa. It has long been known that the organism is pathogenic to primates. Christeller (1922) has recently described a fatal case in the chimpanzee, and Ziemann (1925) a case in a monkey, *Cercocebus fuliginosus*.

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CORRECTION

In the article by Robert F. McCrackan, Kate M. Harman and Emanuel Passamaneck, "Tables of General Application for Verifying Complete Colorimetric Calculations" (ARCH. PATH. **3**:227 [Feb.] 1927), the following errors occurred: page 230 — 3.850, opposite 5, under 15.8, should be 3.950; page 232 — 3.546, opposite 5, under 17.8, should be 3.560; page 235 — 25, under 34, Column D, should be 35.

Notes and News

American Association of Pathologists and Bacteriologists Elects Officers.—At the annual meeting of the American Association of Pathologists and Bacteriologists in Rochester, N. Y., April 15-16, 1927, the following officers were elected: James W. Jobling, president; E. B. Krumbhaar, vice-president; F. B. Mallory, treasurer, and H. T. Karsner, secretary.

Death of David Hough Dolley.—David Hough Dolley, aged 48, professor of pathology in the school of medicine at St. Louis University since 1922, died recently. Dr. Dolley received his degree of doctor of medicine from Johns Hopkins University in 1902. He was professor of Pathology at the University of North Carolina from 1906 to 1910, and at the University of Missouri from 1910 to 1922.

University News, Promotions, Resignations and Appointments.—W. W. C. Topley, who holds the chair of bacteriology and the directorship of the public health laboratory at the University of Manchester, has tendered his resignation, to take effect in September, when he will take up duties as professor of bacteriology and immunology in the new London School of Hygiene and Tropical Medicine.

V. H. Moon has resigned as professor of pathology in the Indiana University School of Medicine to become professor of pathology in Jefferson Medical College, Philadelphia.

Norbert Enzer, assistant in the Morris Institute for Medical Research, Michael Reese Hospital, Chicago, has accepted the position of director of laboratories of Mt. Sinai Hospital in Milwaukee.

Pierre Masson, of the University of Strasbourg, has been appointed professor of pathologic anatomy in the medical faculty of the University of Montreal and pathologist to Notre-Dame Hospital.

In the Indiana University School of Medicine, Elmer Funkhouser has been promoted from instructor to associate in pathology.

Robert A. Keilty has resigned as pathologist at the Geisinger Hospital, Danville, Pa., and will be succeded by Kenneth Fowler of Ann Arbor, Mich.

Gift for Cancer Research at Ann Arbor.—Announcement has been made that the University of Michigan has been given $45,000 a year for five years from July 1, 1927, to be used toward "discovering and promoting scientific knowledge of the causes, prevention and cure of cancer and other growth processes."

Next Meeting of the Pathological Society of Great Britain and Ireland.—The next meeting of the Pathological Society of Great Britain and Ireland will be held in the department of pathology, Welsh National School of Medicine, Cardiff. The days of the meeting will be July 8 and 9, 1927.

The Sir William Dunn School for Pathology at Oxford.—The new building for pathology at Oxford University has been turned over to the university by the Sir William Dunn trustees. The building cost £70,000. It contains every modern facility, and has accommodations for at least fifty students, and individual rooms for twenty-five research workers. An essential purpose is to attract and develop men and women "of the kind whose minds will lend themselves to research."

American Society for Experimental Pathology Elects Officers.—At the meeting of the American Society for Experimental Pathology in Rochester, N. Y., April 14-15, 1927, the following officers were elected: David Marine, president; E. B. Krumbhaar, vice-president, and Carl V. Weller, secretary.

Death of Erwin F. Smith.—Erwin F. Smith, aged 73, pathologist in charge of the laboratory of plant pathology in the U. S. Bureau of Plant Industry, and known to pathologists in general for his work on tumors of plants, died on April 6.

Radiologic Institute at Washington University.—A gift of $1,000,000 to establish a radiologic institute for the study of cancer at Washington University School of Medicine is announced. The work will include the study of the general diagnostic and therapeutic uses of the roentgen ray and other more powerful rays. The donors are the General Education Board, Edwin Mallinckrodt, a chemical manufacturer of St. Louis, and members of his family. Approximately $250,000 will be spent for a four-story building to house the institute, and the remainder will be used as an endowment for research.

American Association of Immunologists Elects Officers.—At the annual meeting of the American Association of Immunologists in Rochester, New York, April 14-15, the following officers were elected: Dr. Karl Landsteiner, president; Dr. A. F. Coca, secretary-treasurer, and Dr. Eugene L. Opie, member of the council.

New Designation of Blood Groups.—The following resolution favoring a new designation of the blood groups was adopted by the American Association of Immunologists in Rochester, April 14, 1927:

RESOLVED, 1. That the existence and use of the two numberings of the blood groups, those of Jansky and Moss, constitutes, in the opinion of the association, a source of confusion and of accident in the selection of blood donors.

2. That the suggestion of Dr. Karl Landsteiner that the numberings of Jansky I, II, III and IV and Moss IV, II, III and I be replaced by the letters O, A, B and AB, expressing the constitution of the blood corpuscles with respect to iso-agglutination, be urgently recommended for general adoption in this country.

Medical Fellowships of the National Research Council.—The Rockefeller Foundation will provide the National Research Council $50,000 a year for five years, beginning Jan. 1, 1928, to establish a new series of fellowships in the medical sciences. The fellowships are to be reorganized on the basis of training in research rather than, as heretofore, for training in teaching as well as in research. Consequently, special emphasis will now be placed on the fitness and interest for research of candidates for appointment as fellows.

Abstracts from Current Literature

Pathologic Physiology

STUDIES IN ANESTHESIA, ANOXEMIA, ANHYDREMIA AND ECLAMPSIA, WITH CERTAIN DEDUCTIONS CONCERNING THE TREATMENT OF ECLAMPSIA. H. J. STANDER, Am. J. Obst. & Gynec. **12**:633, 1926.

Stander studied the effects of anesthesia, anoxemia, narcotics and hypnotics, protein-split products and magnesium sulphate on the blood chemistry and on the changes in the liver and kidneys of dogs. Ether, chloroform, nitrous oxide, ethylene gas and anoxemia (air containing only 7 per cent oxygen) caused certain changes in the chemistry of the blood similar to those seen in eclampsia. There was an increase in blood sugar and the lactic and uric acids, and a low carbon dioxide combining power. The anesthetics produced definite changes in the liver and kidneys, so that their employment in eclampsia would be contraindicated. The carbon dioxide combining power was raised when morphine was given; liver changes did not result when this drug or chloral was used. This seems to justify their use in the treatment of eclampsia. Hypnotics, such as paraldehyde, urethane and veronal, brought about changes in the blood similar to those of the anesthetics and caused generalized changes in the liver. Magnesium sulphate, which has often been used to control the convulsions of eclampsia, caused a decrease in the carbon dioxide combining power, and changes in the liver were noted. Protein-split products such as peptone, albumose and histamine produced the blood picture of anhydremia, and pathologic changes in the liver similar to those found in pernicious vomiting of pregnancy; Stander suggests that such substances may be the etiologic factor in the latter condition. The author advocates a conservative treatment for eclampsia and, when necessary, spinal anesthesia with cocaine or its derivatives, which do not produce changes in the blood or liver as were noted with the other anesthetics.

A. J. KOBAK.

THE CAUSE OF THE DELAYED CLOTTING OF HEMOPHILIC BLOOD. W. H. HOWELL and E. B. CEKADA, Am. J. Physiol. **78**:500, 1926.

In a study of three hemophilic patients, brothers, it was found that the prothrombin content of the blood did not vary from normal either quantitatively or qualitatively. The blood platelets, on the other hand, were much more resistant than those of normal blood, and the authors account for the hemophilia by their slow disintegration.

H. E. EGGERS.

THE ABSORPTION OF BILE PIGMENT FROM THE INTESTINE. J. L. BOLLMAN, C. SHEARD and F. C. MANN, Am. J. Physiol. **78**:658, 1926.

On determining the content of bilirubin in the mesenteric veins and in the arterial circulation of dogs, using the spectrophotometric method, which was sufficiently sensitive to detect any addition of bilirubin in known sites of its formation, essential differences were not found in the two values. This was true regardless of whether the animals were fed more or less recently, or were fasting, or even after the introduction of large amounts of bile into the intestine. Parallel determinations of rose bengal showed much absorption from

the intestine. Farther, introduction of large amounts of bile into animals after common duct ligation and gallbladder extirpation did not have any effect on the rate of developing jaundice. The authors state definitely that there is not any intestinal absorption of bilirubin under their experimental conditions.

H. E. Eggers.

Intragastric Leucopedesis. H. C. Hou, Am. J. Physiol. **79**:28, 1926.

In dogs with Heidenhain, or Pawlow pouches, and some splenectomized dogs with Pawlow pouches, and with gastric secretion stimulated either by histamine injections or by feeding, the following results were obtained:

Into the resting stomach there is a constant influx of cells, principally polymorphonuclear leukocytes. The concentration of these cells falls after meals or histamine injections to a minimum in from 30 to 60 minutes, recovering to normal in from two to three hours.

After histamine injection total cell output is raised during the first hour, falling below control values during the second. After meals the increase may be maintained for from two to five hours.

The diminished concentration is due to dilution by the active hydrochloric acid secretion.

Constant relationship could not be shown between intragastric leukopedesis and peptic activity of the gastric juice, nor apparently to proteolytic ferment content of blood. Connection could be shown between this leukopedesis and blood leukocytosis.

H. E. Eggers.

Cretinism and Myxedema Produced Experimentally in Swine. H. D. Caylor and C. F. Schlotthauer, Am. J. Physiol. **79**:141, 1926.

Because of peculiarities in anatomy and physiology, swine were found satisfactory animals for the production of experimental myxedema and cretinism. They responded quickly to thyroid deficiency with definite symptoms. Distinct parathyroids were not found, islands of parathyroid tissue being located in accessory thyroids. Tetany did not develop in animals completely thyroidectomized. A more marked reaction developed in animals operated on before puberty. There was an apparent hypersusceptibility to disease in thyroidectomized animals.

H. E. Eggers.

The Diuretic-Antidiuretic Action of Pituitary Extract. R. L. Stehle, Am. J. Physiol. **79**:289, 1927.

Based on a study of the urinary excretion of alkali and alkaline earth salts after the administration of pituitary extract, the writer reaches the following conclusions:

The action of pituitary extract in influencing volume of urinary excretion is chiefly or wholly a sequence of a primary action on body tissues. This is concluded from the fact that there is an extraordinary increase in the content of salts of potassium, calcium, magnesium and phosphorus — all presumably derived from tissue cells. He suggests that the diuresis is purely a salt effect, made necessary to eliminate the salts thrown into the blood from the tissues.

The antidiuretic action of pituitary extract seen when its administration is preceded by the preliminary administration of water he regards as explainable on the basis of increased capacity of the tissues to hold water as a result of electrolytic changes.

He further suggests that in diabetes insipidus there is a reversed condition as regards electrolytic changes, which decreases the ability of the body to hold water.

H. E. Eggers.

Studies on Diabetes Insipidus. I. H. Bourquin, L. C. Benesh and M. O. Lanam, Am. J. Physiol. **79**:362, 1927.

Diabetes insipidus was produced in dogs by the cauterization of the mammillary bodies at the floor of the third ventricle. Caused in this way, it is to be regarded as an irritation rather than a deficiency phenomenon, as it followed slight, but not severe, injury.

The following evidence is deduced for the view that the diuresis is due to the production of some substance locally as a result of the injury:

That the hypophysis is not responsible is shown by the fact that when it is excised without injury to the proper area of the floor of the third ventricle diabetes insipidus is not produced. If in such animals that area is injured, diabetes insipidus ensues.

The thirst of diabetes insipidus is secondary to the diuresis, since this occurs in animals restricted to their preoperative water intake, and such animals quickly give evidence of desiccation.

Independence of the phenomenon of the autonomic and somatic nervous systems is shown by the fact that typical diabetes insipidus caused by ventricular irritation occurs after the transection of the spinal cord at the level of the eighth cervical vertebra, double vagotomy below the diaphragm and paralysis of the parasympathetic nervous system by atropine.

With cross transfusions between severely diabetic and normal animals, brief diuresis was observed in some cases. This result was never obtained in the cross transfusion of normal animals.

H. E. Eggers.

Pituitrin and Diuresis in Man. E. F. Adolph and G. Ericson, Am. J. Physiol. **79**:377, 1927.

The intramuscular injection into man of pituitary extract, at the same time that various solutions were taken by mouth, did not affect the excretion of the solutes.

The extra excretion of water, after the ingestion of pure water, was completely inhibited. If salts were ingested more concentrated than the maximal excretory concentration, this inhibitory effect was not observed.

Following the ingestion of isotonic solutions of potassium chloride and urea, pituitary extract allowed the excretion of the excess of water required for salt diuresis, the remainder being retained.

Hence, pituitary extract evidently renders the kidneys insensitive to an excess of water in the blood plasma—a fact which helps distinguish diuresis due to dilution from that caused by salt excretion.

H. E. Eggers.

Functional Liver Tests in Massive Hepatic Trauma. L. A. Levinson and E. J. McCormick, Ann. Clin. Med. **5**:483, 1926.

In a case in which the greater part of the liver was destroyed by crushing trauma, and in which the gallbladder was ruptured, tests for liver function were normal.

Walter M. Simpson.

CONTRIBUTION TO THE STUDY OF TOXIC ABSORPTION FROM THE INTESTINAL TRACT IN EXPERIMENTAL HIGH OBSTRUCTION. LOUIS BRAEYE, Bull. Johns Hopkins Hosp. **40**:33, 1927.

The passage of toxins from an obstructed isolated loop of dog intestine was not influenced appreciably by soap or bile.

THE DISABILITIES CAUSED BY HYPOPHYSECTOMY AND THEIR REPAIR; THE TUBERAL (HYPOTHALAMIC) SYNDROME IN THE RAT. PHILIP E. SMITH, J. A. M. A. **88**:158, 1927.

Hypophysectomy produces an invariable and characteristic syndrome in the rat, the chief features of which are an inhibition in growth in the young animal or a loss of weight in the mature animal, atrophy of the thyroids, suprarenal cortex and sex organs, weakness and cachexia. The animal survives for months.

The disabilities arising from hypophysectomy can be completely or nearly completely cured by daily pituitary homotransplants. Intraperitoneal injections of saline extracts (suspensions) made from ox pituitaries prepared by the method of Evans and Long do not repair the atrophied thyroids or suprarenal cortex; and these injections not only do not repair the atrophied sex organs but also prevent their repair by the pituitary transplants. Skeletal growth is stimulated by injection of the bovine fluid.

A lesion of the hypothalamic region of the brain (tuber cinereum) gives rise to a syndrome which is distinct from that caused by pituitary ablation. This tuberal syndrome is characterized by extreme obesity and an atrophy of the genital system; neither the thyroids nor the suprarenal cortex atrophy. In certain cases the total length of these animals may be reduced; in other cases it is unaffected.

AUTHOR'S SUMMARY.

THE RELATIVE REACTION WITHIN LIVING MAMMALIAN TISSUES. PEYTON ROUS, D. R. DRURY and W. W. BEATTIE, J. Exper. Med. **45**:23, 1927.

The changes in blood reaction caused by the injection into a vein of a weak solution of hydrochloric acid are accompanied by extravascular changes of similar magnitude within the subcutaneous tissue. Under the conditions of prolonged general anesthesia with ether or urethane the circulation to this tissue is so interfered with that an "outlying acidosis" may develop in addition to the acidosis immediately consequent on the blood state. Even under the best of circumstances the extravascular acidosis induced with hydrochloric acid affects not merely the tissue fluid but also the reaction of the tissue itself.

Rabbits in which a widespread extravascular acidosis has been produced, together with a blood acidosis as severe as is compatible with life, remain in good condition during the relatively long period over which this state of affairs persists. Signs of capillary dilation and of shock are not present at any time, though the vessels are bathed in relatively acid fluid. Edema does not develop in the acidotic tissues, and the animals void large amounts of urine. The tissue acidosis lessens pari passu with that of the blood.

AUTHORS' SUMMARY.

THE RELATIVE REACTION WITHIN LIVING MAMMALIAN TISSUES. D. R. DRURY, W. W. BEATTIE and PEYTON ROUS, J. Exper. Med. **45**:41, 1927.

Breathing an atmosphere that contains the normal amount of oxygen but a large excess of carbon dioxide results in a tissue acidosis as well as one of the blood. The extravascular changes in reaction take place with far greater

speed than when acidosis is induced with hydrochloric acid, and they do not persist as in the case of this latter but swiftly disappear when the animal breathes ordinary air again. The changes parallel closely in magnitude and time those occurring in the blood. The same matrix tissues are rendered acidotic as when hydrochloric acid is administered.

The blood alkalosis that results from a blowing off of carbon dioxide is accompanied by an extravascular alkalosis. Under the circumstances of the experiments the connective tissue became more alkaline than ordinary but change was not noted in the cartilage, a fact to be explained by the slight degree of the alkalosis and its brief duration. AUTHORS' SUMMARY.

STUDIES IN BLOOD COAGULATION. C. M. VAN ALLEN, J. Exper. Med. **45**:69 and 87, 1927.

A description is given of the methods used in studying changes in blood coagulability in various diseases of the rabbit, including malignant tumors, infection and nonbacterial diseases.

EXPERIMENTAL OBSERVATIONS ON IRRADIATED NORMAL AND PARTIALLY PARATHYROIDECTOMIZED RABBITS. FREDERICK L. GATES and J. H. B. GRANT, J. Exper. Med. **45**:115, 125 and 139, 1926.

The experiments described in the three papers of this series were undertaken to determine if possible the significance of the parathyroid hypertrophy that has repeatedly been found in rabbits after exposure to ultraviolet light. The fact that the hypertrophy was not accompanied by a corresponding increase in blood calcium led us to infer that the upper level of blood calcium concentration is governed by factors independent of parathyroid control, and that the gland hypertrophy under the influence of ultraviolet light might represent a potential functional capacity, or increased factor of safety, to protect the calcium level under conditions of stress or emergency. Partial parathyroidectomy in irradiated rabbits, compared with the same operation in normal controls, resulted in a similar immediate drop in blood calcium; but a more rapid restoration of the calcium level in the irradiated rabbits indicated a more prompt and active response to the emergency on the part of the remaining glands. In the second group of experiments significant differences were not found in the reactions of irradiated, normal or partially parathyroidectomized rabbits to injections of calcium chloride or of disodium hydrogen phosphate. All three groups of rabbits rapidly eliminated the excess calcium from the blood. Their reactions to large doses of sodium phosphate, given subcutaneously, appeared to be related to phosphate elimination or retention in the individual animals. In each group, those that had phosphate retention in the blood died in acute tetany.

So also in the fasting experiments reported in this paper, distinctions could not be drawn between normal, irradiated and partially parathyroidectomized rabbits on the basis of their calcium and phosphorus metabolism. Blood calcium was reduced in a similar manner in all three groups of rabbits, and wide individual variations in serum phosphorus levels preclude significant deductions.

But the irradiated rabbits suffered disproportionate losses of weight during the fasting period, and four of five of them died during the course of the experiment. The deaths of these rabbits are attributed to this more rapid consumption of their own tissues and possibly also to suprarenal injury caused both by fasting and by exposure to ultraviolet light. AUTHORS' SUMMARY.

THE EFFECT OF HIGH PROTEIN DIET ON RENAL FUNCTION. H. MACLEAN, J. FOREST SMITH and A. L. URQUHART, Brit. J Exper. Path. **7**:360, 1926.

High protein feeding when accompanied by a little green food produces temporary changes in the metabolism of the rabbit, which are indicated by a marked rise in blood urea and urine urea. If this high protein diet is continued, these changes are no longer in evidence after about a month. The renal mechanism apparently adapts itself to the increased nitrogenous intake, so that examination of both blood and urine for nitrogenous waste products gives normal results.

A high protein diet, when a little green food is given also, does not give rise to any changes of the nature of nephritis in the rabbit's kidney. The same diet in the absence of all green food quickly produces marked albuminuria, accompanied by the presence of abundant casts in the urine. This condition is quickly relieved if a small amount of green food is given, but if green food is persistently withheld for some time after the nephritis is established, the animal dies. Not in any case could evidence of chronic inflammatory changes be found on microscopic examination of the kidneys of such rabbits.

There is not any evidence that high protein diet has deleterious effect on the kidneys of the rabbit; indeed, the kidneys soon adapt themselves to the new conditions. The absence of green food in the diet, however, soon results in the production of nephritis no matter what the protein content of the diet happens to be. These facts may have some bearing on the treatment of nephritis, for fresh vegetables may be more important than the usual abstention from protein food.

AUTHORS' SUMMARY.

STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM. PART 4. THE INFLUENCE OF FREE FATTY ACIDS IN THE INTESTINE ON THE ABSORPTION AND EXCRETION OF THE MINERAL ELEMENTS. S. V. TELFER, Quart. J. Med. **20**:1, 1926.

In a case of catarrhal jaundice fat absorption was reduced by 20 per cent during the period that bile was excluded from the intestines. There was then an increase in fatty derivatives and calcium soaps. The absorption of phosphoric acid was increased as shown by the high phosphoric content in the urine. This was due to the combination of calcium with soaps reducing the amount of calcium phosphate. When the condition was improving, the phosphate of lime increased and as this increased the calcium excreted decreased, showing that linkage of calcium with fatty acids prevented the absorption of the phosphate of lime. In a previous article the author had shown that conditions which permit of excretion of free fatty acids in the intestine facilitate the absorption of phosphorus.

N. ENZER.

STUDIES IN CALCIUM AND PHOSPHORUS METABOLISM. PART 5. INFANTILE RICKETS. THE EXCRETION AND ABSORPTION OF THE MINERAL ELEMENTS AND THE INFLUENCE OF FATS IN THE DIET ON MINERAL ABSORPTION. S. V. TELFER, Quart. J. Med. **20**:7, 1926.

During the active stages of the disease, the lime, magnesium and phosphoric content of the feces is high, because of defective absorption due to some change in the intestines. This is reduced when healing takes place. The phosphorus is first absorbed in excess, the urine containing a high percentage.

Cod liver oil has a specific effect in increasing the absorption of the minerals by altering those conditions in the gastro-intestinal tract which prevented their free absorption.

N. Enzer.

The Action of Insulin in Glycogen Formation and Its Therapeutic Application. R. D. Lawrence, Quart. J. Med. **20**:69, 1926.

Exercise increases the hyperglycemic action of insulin, and the combined effect of insulin and exercise is greater in burning carbohydrate than that of exercise alone. Considerable discussion is offered on the metabolism of carbohydrate and fat and the formation of glycogen and on the specific action of insulin. The author considers that insulin does not really burn carbohydrate but changes it into glycogen and that its main function is to provide for glycogen storage. In diabetes, the increased tolerance to insulin is probably due to the increased storage of glycogen. The hypoglycemic action of insulin is, therefore, much more marked when glycogen storage is decreased. The studies were made on a diabetic patient who was well trained and who understood the principles of diet and exercise. Hypoglycemia was constantly produced by violent exercise plus the patient's regular dosage of insulin.

N. Enzer.

The Effect of a Continued Polyuria Upon the Kidney of the Rat. C. S. Hicks and M. L. Mitchell, Australian J. Exper. Biol. & M. Sc. **3**:221, 1926.

Adult rats were sustained on the normal balanced dietary of casein, potato, starch, butter, sucrose and salt mixture, plus marmite; to this mixture was added common salt in increasing quantities until 15 per cent was reached. Water was consumed continually, and a marked polyuria resulted. However, impairment of kidney function had not resulted after four months, and the kidneys did not then show any abnormal changes. The livers of the animals increased to double the normal size and weight, because of increased vascularity and possibly hypertrophy. The blood ammonia in four animals tested was increased to six times the normal.

Pathologic Physiology and Therapeutics of Circulatory Disturbances in Asystole. Lucien Dautrebande, Arch. internat. de med. exper. **2**:413, 1926.

This lengthy article is preceded by a discussion of the hydrogen ion concentration of venous and arterial blood, the general theory of gaseous metabolism and interchange and a long summary of clinical cases. The real work comes in the discussion of the influence of heat and cold locally applied. The author summarizes the first chapters in the following manner: The slowing of the circulation in cardiac conditions without valvular lesions causes a drop in the alkaline reserve and in the hydrogen ion concentration of venous blood and a corresponding elevation in the arterial blood. The hemoglobin concentration is higher in the venous blood. A single examination of the blood is not sufficient to detect this change in the alkaline reserve in cardiac decompensation, because the drop may be masked by a pulmonary element, such as emphysema, which occurred before the decompensation. Cold baths applied to an extremity cause slowing of the circulation both in experimental cases and in clinical cases, with a resulting concentration of the hemoglobin and a temporary elevation of the amount of carbonic acid liberated, and therefore

a fall in the alkaline reserve. The arterial blood is, therefore, found in a state of alkalosis, and this brings about an increased pulmonary ventilation as a result of stimulation of the respiratory center by the increased alkalinity of the blood. The cardiac output diminishes for the time, until the respiratory center responds and brings about superventilation of the blood. Hot local applications do not have the same action. A local application of 45 C. doubles the cardiac output, the degree of increase depending on the amount of the skin submerged and on the temperature. In such cases the buccal temperature is elevated and the blood arriving at the heart has a higher temperature than normal. In addition to this the venous pressure is increased. In his conclusions he finds the characteristics of blood stasis in cardiac decompensation to be acidosis of the venous blood and alkalosis of the arterial blood. The treatment of this cardiac disturbance is to avoid the blood stasis and to bring about a normal acid-base equilibrium between the arterial and the venous blood. Local hot applications experimentally produce this effect, and the clinical application of heat seems to have considerable benefit.

N. Enzer.

The Hypoglycemic Action of Sulphur. D. Campanacci and R. Balducci, Klin. Wchnschr. **5**:2166, 1926.

Subcutaneous injection of colloidal sulphur reduces the blood sugar. In diabetic patients the action is slower and less marked, but of longer duration, than that of insulin. Sulphur also increases the alkaline reserve of the blood and stops acetonuria and glycosuria. Colloidal silver and colloidal manganese do not have such an action.

J. D. Willems.

Ovarian Hormone, Genital Growth and Sexual Precocity. B. Zondek and S. Aschheim, Klin. Wchnschr. **5**:2199, 1926.

A water soluble substance containing the hormone is prepared from the ovary and called folliculin. When this substance is injected into virginal mice the animals go into heat, and the uterus increases in size and weight up to four times that of the control animals.

J. D. Willems.

The Ability of the Human Blood to Form Lactic Acid from Polysaccharides. A. Abraham and S. Friedberg, Klin. Wchnschr. **5**:2264, 1926.

Glycogen, starch and dextrose are mixed with defibrinated human blood and incubated from six to eight hours at 37 C., and then examined quantitatively for lactic acid. The lactic acid production from dextrose always far exceeds that from glycogen and starch.

J. D. Willems.

A Singular Case of Lipomatosis Atrophicans. F. Strieck, München. med. Wchnschr. **73**:2029, 1926.

A megalocephalic girl, aged 6 years, nearly normal in size and weight, mentally bright and generally healthy had large tumor-like pads of fat distributed over the body with some degree of symmetry. Since the age of 2 years she had eaten as much as an adult and had a greatly increased basal metabolic rate.

The relationship of these various conditions is not discussed and an explanation is not given.

J. D. Willems.

Pathologic Anatomy

DEPOSITION OF DYES, IRON AND UREA IN THE CELLS OF A RENAL TUBULE AFTER THEIR INJECTION INTO ITS LUMEN: GLOMERULAR ELIMINATION OF THE SAME SUBSTANCES. J. M. HAYMAN, JR., and A. N. RICHARDS, Am. J. Physiol. **79**:149, 1926.

A number of dyes, a salt of iron and urea were introduced into the lumens of the renal tubules of living frogs by injection with a capillary pipet into the intracapsular space of Bowman's capsule. In all cases the amounts used were too small to give any demonstrable effect if injected into the blood stream. In every instance the injected material could be identified within the tubular epithelium, corresponding in manner and amount with its deposition there after injections of larger amounts into the blood stream.

Each of the substances was present in the glomerular fluid after injection into the circulation.

The authors consider that discovery of intravenously injected material in microscopic sections of kidney does not constitute evidence of its secretion through the tubules, unless it can be proved that the material does not pass through the glomerular membranes.

H. E. EGGERS.

ISCHAEMIC CONTRACTURE. P. N. Jepson, Ann. Surg. **84**:785, 1926.

An injury in the region of a joint, whether a fracture or merely damage to the soft parts, frequently leads to the condition known as ischemic contracture. This results in those cases in which venous stasis has been produced and in which the muscles and nerves consequently have been compressed by exudate of serum and by hemorrhage. Nerve atrophy may result. If drainage of the soft tissues is instituted early the resulting contracture will be slight. The lesion was produced in dogs by prolonged bandaging of a limb in which the femoral vein had been ligated, and the lesion could be prevented from developing if the hemorrhagic and serous exudate was drained.

N. ENZER.

TUBERCULOSIS OF THE THYROID GLAND. F. A. COLLER and C. B. HUGGINS, Ann. Surg. **84**:804, 1926.

The thyroid is affected in two ways by tuberculosis: miliary and chronic caseating and fibrotic lesions. The latter generally extend beyond the thyroid to the surrounding tissue, resulting in fixation of the gland. The majority of cases occur in adenomatous thyroids and more frequently in normal than in hyperplastic ones. Scirrhous and fibrous atrophy occurs in chronic tuberculosis, but histologically this lesion does not give any evidence of tuberculosis of the thyroid itself; it may produce myxedema. The author contributes five cases and summarizes briefly the literature.

N. ENZER.

THE MODE OF ORIGIN OF GALLBLADDER LESIONS. J. DENTON, Arch. Surg. **14**:1, 1927.

"A fairly extensive review of the literature failed to discover descriptions of infectious lesions of the gallbladder in the absence of stones. Comparison of the gross and microscopic changes in the gallbladder in cases in which cholecystectomy was performed within two or three' days after the impaction of a stone in the cystic duct made it clear that the primary lesions in the gallbladder were intramural edema, venous distention and intramural hemorrhage."

The impaction of the stone closes off the veins and lymphatics before the artery. The material studied comprised 403 cases in which cholecystectomy had been performed; 188 gallbladders contained stones and 121 of these showed pathologic changes. Only 19 of the remaining 215 showed definite pathologic change, and the author considers that these 19 probably had contained stones. "If primary infectious lesions of the gallbladder occur they must be uncommon."

N. ENZER.

SOLID TUMORS OF THE URACHUS. L. BRADY, Arch. Surg. **14**:46, 1927.

Including the author's case, twenty solid tumors of the urachus have been reported. His was a fibromyoma weighing 600 Gm. These tumors occurred more frequently in men than in women. Eighteen of the cases were malignant, seven being sarcomas and eleven carcinomas.

N. ENZER.

A CASE OF MULTIPLE ANEURYSMS OF THE BRANCHES OF THE PULMONARY ARTERY. D. H. SHERMAN and B. ROMAN, Bull. Buffalo Gen. Hosp. **4**:39, 1926.

A boy, aged 7½ years, who died of pneumococcic meningitis after a long period of illness, following appendectomy and purulent peritonitis, exhibited at necropsy in the branches of the pulmonary artery in both lungs altogether five aneurysms, the largest of which measured 1.8 by 3.5 cm. Associated with these were multiple suppurative pulmonary infarcts, and a typical congenital subaortic septum perforation in the heart, accompanied by endocarditis. Because of the latter, the absence of syphilis and the microscopic structure of their walls, the aneurysms were assumed to be of infective nature, their development having been favored by the increased pressure in the pulmonary artery due to the perforated ventricular septum.

AUTHORS' SUMMARY.

A BIOMETRIC STUDY OF THE RELATIVE CELL VOLUME OF HUMAN BLOOD, IN NORMAL AND TUBERCULOUS MALES. RAYMOND PEARL and JOHN RICE MINER, Bull. Johns Hopkins Hosp. **40**:3, 1927.

It seems probable that the presence of active tuberculosis has as one of its associated phenomena a lowering of the relative cell volume of the blood.

THE PATHOLOGY OF DIABETES IN CHILDREN. SHIELDS WARREN, J. A. M. A. **88**: 99, 1927.

The pancreas in diabetic children may be small, but the amount of island tissue is not sufficiently reduced to account for the disturbed metabolism in most cases. Diabetes in children is a severe disease, but one case is presented in which the course of the disease was twenty-nine years, from 9 to 38 years of age. All but one of the patients died in coma, and that one was accidentally killed. Lymphocytic infiltration of the islands, found among children, is a lesion not encountered in older diabetic patients, and hyalinization of the islands is not found in the young. There is little pathologic change in either islands or acinous tissue, though commonly reported in the old, and that present does not appear sufficient to account for the marked disturbance in function. Consideration of the anatomic pathology of diabetes in children leads to the hope that, through treatment which allows the element of time to act, irreversible changes in the pancreas may be avoided.

AUTHOR'S SUMMARY.

STUDIES ON RED CELL DIAMETER. J. R. BELL, F. K. THOMAS and J. H. MEANS, J. Clin. Investigation **3**:229, 1926.

Diameters of the red cell population of the blood of normal persons follow the law of natural frequency. The medians and dispersions of such curves are remarkably alike among different subjects. In pernicious anemia there is a striking increase in both these functions. This fact is of diagnostic significance in distinguishing between pernicious and other types of anemia.

AUTHORS' SUMMARY.

THE ASSOCIATION OF GENERALIZED ARTERIOLAR SCLEROSIS WITH HIGH BLOOD PRESSURE AND CARDIAC HYPERTROPHY IN CHRONIC NEPHRITIS. ARNOLD BRANCH and GEOFFRY C. LINDER, J. Clin. Investigation **3**:299, 1926.

This report is based on clinical and anatomic observations in ten young subjects (under 34) with chronic glomerulonephritis. Three patients died of intercurrent infections, seven came to death from typical nephritis, six died from uremia and one from heart failure.

The three cases (in children aged 3, 3 and 14 years) which terminated by intercurrent infection showed relatively mild but definite, diffusely distributed glomerular lesions. They were free from hypertension, arteriolar sclerosis or cardiac hypertrophy, and demonstrate that glomerulonephritis can develop to a considerable degree without such results.

All seven cases which progressed to typical nephritic deaths showed hypertension and neuroretinitis, together with cardiac enlargement, gross in five cases, moderate but probably definite in two. These observations accord with the current view that cardiac enlargement in nephritis is the result of hypertension.

In six of the seven cases arteriolar sclerosis of the parenchymatous organs was found at autopsy. The concurrence of arteriolar sclerosis so frequently with retinitis and hypertension shows that the presence of hypertension in nephritis indicates usually but not always a coexisting arteriolar sclerosis.

The nonconforming case (case 4) confirms Volhard and Fahr (5, p. 41) in showing that arteriolar sclerosis may be absent even when neuroretinitis and hypertension have existed for several months, accompanied by renal insufficiency advancing to uremia.

AUTHORS' SUMMARY.

CHILD LIFE INVESTIGATIONS. A CLINICAL AND PATHOLOGICAL STUDY OF 1,673 CASES OF DEAD-BIRTHS AND NEONATAL DEATHS. EARDLEY L. HOLLAND and JANET E. LANE-CLAYPON, Special Report Series, No. 109, Medical Research Council, 1926.

The frequency of intracranial lesions was high in this series. Tentorial tears were noted in just over one fourth of all cases of fresh and neonatal deaths. Of these, some occurred in spontaneous breech labor, with, in some cases, difficulty in the delivery of arms or head; but the majority were associated with delivery by forceps or podalic version.

HEREDITARY EYE-DEFECTS IN RABBITS, EXPERIMENTALLY INDUCED. FREDERIC ALLISON DAVIS, Tr. Ophth. Soc. **45**:555, 1926.

This paper consists of a discussion of hereditary eye defects in rabbits, experimentally induced. The material on which the study is based was produced by Guyer and Smith of the Department of Zoology of the University of

Wisconsin. The lesions were produced by the injection of lens sensitized serums and pulped lens into pregnant rabbits. The study embraces 152 eyes, of which seventy-five were defective.

The outstanding defects found were as follows: Typical coloboma of the iris, ciliary body, choroid, retina and, at times, optic disk, which was accompanied by varying grades of microphthalmus, with and without cystic staphyloma. The coloboma develops as a result of faulty closure of the fetal ocular cleft. The degree of deformity depends on the extent to which the fetal cleft remains open. The cleft is apparently prevented from closing by the persistence and overgrowth of mesodermal tissue in the cleft. This may extend the entire length of the cleft from the optic disk to the corneoscleral margin, or it may be confined to the posterior end of the cleft or to the anterior end. The lens is affected in varying degrees in most of the eyes. It has apparently remained normal, however, in one 18 day embryo, and in one adult eye in which the coloboma was confined to the extreme posterior end of the cleft. In those eyes showing moderate grades of microphthalmus, the lens is well developed, somewhat enlarged and usually spherical. This latter condition is apparently brought about by the swelling of the fibers as the result of relaxation of the zonule in the colobomatous area. The lens substance is completely absorbed only in those cases of extreme microphthalmus with degeneration of the entire eye. Coloboma of the iris apparently involves all the coats of the iris, and coloboma of it, as well as of the ciliary body and of the choroid, is apparently due to failure of the union of the margins of the optic vesicle in the region of the fetal ocular cleft. The absence of the pigment epithelium apparently affects the development of the underlying structures, namely, the stroma of the iris and the choroid.

The theories as to the cause of the persistence and overgrowth of mesoderm in the cleft are discussed. It is assumed that it is brought about by stimulation or overgrowth of mesodermal elements in the cleft, or that it is due to an arrest of development in the advancing optic vesicle brought about through the specific action of an ectodermal antigen, namely, the lens. This latter theory might be further substantiated by the thinned out appearance of the nervous layer of the retina at the margins of the cup. This might represent an abiotrophy of this structure brought about by a specific immunologic reaction. With the acceptance of the latter view, overgrowth of the mesoderm might be regarded as a process of repair in an effort to close the open fetal cleft.

Defective specimens were presented showing the anomaly at various stages. The ages of the animals from which defective eyes were exhibited included embryos of 18 days up to the fully developed animal of 4 or 5 years. A large number of specimens were shown of the new-born rabbit. F. A. Davis.

The Rôle of the Reticulo-Endothelial System in the Regulation of the Number of Platelets in the Circulation. S. P. Bedson, Brit. J. Exper. Path. **7**:317, 1926.

The temporary upset in function of the reticulo-endothelial cells produced by filling them with carbon particles, Bedson avers, is associated with a considerable increase in the number of platelets in the circulation. Removal of the spleen when blockade of the reticulo-endothelial system is at its height of functional activity is not productive of any further rise in the platelet count. The spleen would appear to regulate the number of platelets in the circulation by means of its reticulo-endothelial cells. In view of the essentially phagocytic

nature of these cells, it seems reasonable to suppose that they take up and destroy the platelets which are not any longer of use. When the spleen is removed, this function is taken on by some other portion of the reticulo-endothelial system.

AUTHOR'S SUMMARY.

THE PATHOLOGICAL EFFECTS OF HYPNOTIC DRUGS UPON THE CENTRAL NERVOUS SYSTEM OF ANIMALS. FREDERICK A. MOTT, D. L. WOODHOUSE and F. A. PICKWORTH, Brit. J. Exper. Path. **7**:325, 1926.

The animals used by Mott et al. were cats and monkeys. The drugs administered belong to two groups, the sulphone and the barbitone. The drugs were given by mouth. When these hypnotic drugs were administered over a period of seven or more days, numerous masses of a peculiar mucinoid material, from 5 to 60 microns in diameter, are found distributed throughout the central nervous system. Normal control tissue gives complete absence of this material. The fixed material in its staining reactions shows properties somewhat similar to amyloid. Chromatolysis, loss of Nissl substance and signs of cell degeneration are present in the nerve cells of the cerebellum, midbrain and spinal cord after intensive treatment with any of the hypnotic drugs. The cell degeneration is accompanied by the appearance of numbers of phagocytic cells, which appear to digest the nerve cells.

AUTHORS' SUMMARY.

METHOD FOR DETERMINING THE ANTISCORBUTIC VALUE OF A FOODSTUFF BY MEANS OF HISTOLOGICAL EXAMINATION OF THE TEETH OF YOUNG GUINEA-PIGS. AXEL HÖJER, Brit. J. Exper. Path. **7**:356, 1927.

In the absence of scurvy cross-sections of the incisor root show in hematoxylin-eosin sections a broad, uniformly stained pink layer of dentine, a white, uncalcified predentine, a layer of slender parallel odontoblasts and a pulp of small, star-shaped cells. When deficient or no antiscorbutic is furnished in the diet, the picture becomes different: The dentine is not stained uniformly and is rather thin; the predentine stains deeply with hematoxylin because it is calcified, and the odontoblasts are changed in shape and arrangement.

A CASE OF OSTEOGENESIS IMPERFECTA. DONALD HUNTER, Lancet **1**:9, 1927.

A case is recorded with blue sclerae. The family history was negative. Corresponding to the early onset at the age of 3 weeks there is dwarfism and deformity of the skull. The long bones have been fractured at least thirty times without violence. Roentgenograms show the classic shape of the skull; the long bones are short and bowed and show an extremely thin corticalis and faint spongiosa. The blood serum calcium and inorganic phosphate were normal.

A CASE OF DILATED COLON SIMULATING PNEUMOTHORAX. H. CARPENTER, Tubercle **8**:107, 1926.

This is a clinical and roentgenologic report of a case in which pneumothorax was completely ruled out; an abnormal dilatation of the splenic flexure of the colon, accompanied by gastroptosis, was demonstrated. The patient's symptoms of bronchial catarrh were of a minor character and were not related to the condition found.

H. J. CORPER.

THE FAT METABOLISM IN THE LUNG. REHBERG, Beitr. z. Klin. d. Tuberk. **64**:718, 1926.

The normal lung shows histologically the signs of a certain amount of lipolytic action; this is evident particularly in animals that receive cod liver oil orally, intratracheally or intravenously. In lungs which have been collapsed by artificial pneumothorax the lipolysis was definitely more pronounced.

MAX PINNER.

THE CHANGES IN THE GASTRIC MUCOSA IN PULMONARY TUBERCULOSIS. T. H. SCHNIDER, Beitr. z. Klin. d. Tuberk. **64**:734, 1926.

In ten cases of chronic pulmonary tuberculosis, picked at random, definite pathologic changes in the gastric mucosa were demonstrable. A chronic gastritis was always present; in three cases a pronounced gastritis with atrophy was observed. In only one case was a tubercle found at the pylorus. There was not any apparent parallelism between the pathologic alterations in the stomach, on the one hand, and the duration of the tuberculosis, the extent or character of the pulmonary process and the temperature curve, on the other hand.

MAX PINNER.

THE RELATION BETWEEN TUBERCULOSIS AND PNEUMOCONIOSIS. F. EICKENBUSCH, Beitr. z. Klin. d. Tuberk. **64**:750, 1926.

The clinical and autopsy records of five patients suffering from a combination of pneumoconiosis and pulmonary tuberculosis are reported. The author comes to the conclusion that even small tuberculous foci greatly enhance the spread of the pneumokoniotic induration, and that usually for a long time the tuberculosis is masked by the pneumokoniosis, which influences the tuberculous processes to a more fibrotic development. Only shortly before death does the tuberculosis as a rule assume an ulcerative and destructive character. The indurations found in such combination cases are probably due both to the mechanical irritation and to tuberculosis.

MAX PINNER.

FEMORAL ARTERIOVENOUS ANEURYSM FROM A RETROGRADE HYPERNEPHROMA METASTASIS. W. MANN, Centralbl. f. allg. Pathol. u. path. Anat. **38**:533, 1926.

In a 72 year old man with a positive blood Wassermann reaction, death resulted from rupture of a large left femoral arteriovenous aneurysm. Post mortem there were found: a hypernephroma on the left side containing many atypical spindle cells; similar spindle cells in the sac of the aneurysm, especially at the junction of the artery and the vein; and no syphilitic changes of the aorta. In view of a lack of venous valves in the region the author explains the aneurysm on a basis of retrograde venous embolism.

GEORGE RUKSTINAT.

SPONTANEOUS FAT TISSUE NECROSIS AND FAT GRANULOMA. A. ABRIKOSSOFF, Centralbl. f. allg. Pathol. u. path. Anat. **38**:542, 1926.

Abrikossoff noted the spontaneous appearance of focal fat tissue necrosis and fat granuloma as painful subcutaneous nodules in convalescents from typhus and relapsing fevers from a few weeks to one and one-half years after their illness. Similar nodules occurred also in the skin, retroperitoneal tissues,

mesentery and omentum in the corpses of obese persons who died from a variety of chronic diseases but in which alterations in the pancreas were not observed. Presumably toxic influences and vascular disturbances cause the necrosis, after which the free and saponified fat plays the rôle of foreign body and calls forth a foreign body giant cell reaction. The cells then absorb the fat. These foci originate in the patient's fat and are not dependent on foreign fats such as injections of camphorated oil.

GEORGE RUKSTINAT.

GAUCHER'S DISEASE AND DISEASES RESEMBLING IT. L. PICK, Ergebn. d. inn. Med. u. Kinderh. **29**:520, 1926.

Following a historical summary of Gaucher's disease, Pick tabulates the data on thirty-nine cases proved by examination of autopsy material in twenty-nine cases, and of operative specimens in eighteen. The maximum weight for the spleen in an adult was 8,100 Gm.; the average weight of twenty-four was 2,700 Gm. The material was from twenty-five females and fourteen males; the youngest patient was a girl, aged 8 months. In one third of the cases there was a tendency for the disease to occur in several persons in one generation. The characteristic alteration in the reticulo-endothelial system of the spleen, liver, lymph glands and bone marrow is the deposition in the Gaucher cells of an optically and chemically indifferent Gaucher substance. This, according to Epstein and Lieb, is probably a cerebroside and is the result of some metabolic disturbance. The best stains for demonstrating Gaucher cells are Mallory's phosphomolybdic acid, anilin blue and orange G. method; Weigert's iron-hematoxylin, and the Bielschowsky-Maresch stain.

Lipoid cell hyperplasia in the spleen of diabetic patients dying in coma with a high lipemia is easily differentiated from Gaucher's disease by the demonstration of neutral fats and cholesterin esters in the cells. The lipoid cell splenohepatomegaly of Niemann can be recognized by its rapid course, phosphatid content of the blood and alterations in the thymic body and suprarenal glands.

GEORGE RUKSTINAT.

CONCERNING THE QUESTION OF EPINEPHRINE LEUKOCYTOSIS AND THE MECHANISM OF ITS ORIGIN. W. M. NOWODWORSKI, Folia haemat. **33**:7, 1926.

Harvey was the first to describe the occurrence of a leukocytosis following the subcutaneous injection of epinephrine hydrochloride. This phenomenon has been repeatedly verified and confirmed by different authors. Nowodworski investigated the leukocytic count in patients with malaria tropica and malaria tertiana. He was interested in this particular disease because he noticed that injections of epinephrine hydrochloride lead practically always to a marked decrease in the size of the spleen in patients with malaria.

His conclusions follow: The suprarenal leukocytosis can be divided into three phases — (*a*) the first phase which begins at the very moment of injection and lasts for about fifteen minutes, and leads to an increase of all forms of white cells; (*b*) the second period, which follows the first, lasts also for about fifteen minutes, leading predominantly to a lymphocytosis; (*c*) the third phase which lasts about two hours and is characterized by an increase in the number of neutrophile leukocytes. He explains this phenomenon on the basis of the spasm of the smaller arteries and also of the smooth muscle of the spleen due to injections of epinephrine hydrochloride, which lead to contraction of the organ with the expulsion of lymphocytes.

B. M. FRIED.

COMMENTS ON PERIARTERITIS NODOSA. G. GRUBER, Zentralbl. f. Herz-u. Gefässkrankheiten **18**:1, 1926.

Gruber elaborately tabulates the data on seventy cases of periarteritis nodosa reported between 1910 and 1926. In a total of 108 cases, the disease lasted from six days to one and one-half years and occurred twenty-six times in the third decade and thirty-one times in the fourth decade, although the age range was from two and a half to seventy-eight years. Males were attacked four times as frequently as females. The process localized in the kidneys eighty-three times, the heart seventy-three times, the liver sixty-six times and the gastro-intestinal tract fifty times, but the synovial membranes were affected only once. Mention is made of the occurrence of the disease in the dog and steer once and in the hog four times. Gruber apparently accedes to the hypothesis that periarteritis nodosa is a constantly similar histologic manifestation of a variety of toxic-infectious diseases. Streptococci have been demonstrated as probably causative in 10 per cent of the cases.

GEORGE RUKSTINAT.

IDIOPATHIC AMYLOIDOSIS. H. SILWER and A. F. LINDBLOM, Acta med. Scandinav. **64**:529, 1926.

A man, aged 34, developed dyspnea, palpitation on exertion, edema of the feet and ankles, cyanosis of the lips and cheeks and increase in size of the abdomen. These symptoms disappeared a few days after admission to the hospital, but the heart and liver remained enlarged. The reflexes and the urine were normal. The patient developed a psychotic condition and died ten months after the appearance of the first symptoms. The necropsy revealed amyloidosis of the heart and kidneys without apparent cause.

Pathologic Chemistry

THE PATHOGENESIS OF BILIARY CALCULI. S. MENTZER, Arch. Surg. **14**:14, 1927.

Disturbance of cholesterol metabolism, general or local, is probably the prime factor in the formation of gallstones, although infection and stasis are certainly contributory factors. It seems certain, too, that a nucleus is essential, for all stones examined contained one. In the formation of the cholesterol stones, the nucleus is frequently a small bit of mucosa loaded with cholesterol, such as occurs in the "strawberry gallbladder." A change in the p_H of the bile toward alkalinity causes a precipitation of the cholesterol.

N. ENZER.

THE SOLUBLE SPECIFIC SUBSTANCE OF PNEUMOCOCCUS: IV. ON THE NATURE OF THE SPECIFIC POLYSACCHARIDE OF TYPE III PNEUMOCOCCUS. M. HEIDELBERGER and W. F. GOEBEL, J. Biol. Chem. **70**:613, 1926.

The "soluble specific substance" of type III pneumococcus may be a polysaccharide of a new type, built up of units of an aldobionic acid, $C_{12}H_{20}O_{13}$.

ARTHUR LOCKE.

ON LIVER AMYLASE AND ITS PROBABLE RÔLE IN THE REGULATION OF BLOOD SUGAR. H. A. DAVENPORT, J. Biol. Chem. **70**:625, 1926.

Insulin and epinephrine hydrochloride do not have any consistent or noteworthy effect on the activity of extracted liver amylase in vitro.

ARTHUR LOCKE.

STUDIES IN THE DISTRIBUTION OF CHLORIDE AND PROTEIN BETWEEN PLASMA AND SYNOVIAL FLUID. F. FREMONT-SMITH and M. E. DAILEY, J. Biol. Chem. **70**:779, 1926.

The distribution of chloride and protein between plasma and synovial effusions has been studied in nineteen instances. These data indicate that the equilibrium between plasma and synovial effusion is of the same nature as that between plasma and peritoneal or pleural effusions.

AUTHORS' SUMMARY.

URINARY CHLORINE AND BASES IN NEPHRITIS. LOUIS LEITER, J. Clin. Investigation **3**:253, 1926.

The urinary chloride concentration test of de Wesselow was studied under controlled conditions on three patients differing in age, general health, type of nephritis and state of renal function. The maximum chloride concentration obtained when the patients were consuming from 5 to 6 Gm. of salt per day varied from 0.28 per cent chloride in case 1 to 0.57 per cent in case 3. With a salt-free diet the values ranged from 0.07 per cent chloride in case 1 to 0.32 per cent in case 3. The urea concentration index and phenolsulphonphthalein were unaffected by the changes in salt intake. The results of the de Wesselow test, even when not complicated by the extrarenal factors present in edema, evidently depend greatly on the salt content of the diet during the days preceding the test. Comparison of the results obtained with the different patients after diets of similar salt content shows a rough tendency for the chloride concentrating power, indicated by the de Wesselow test, to follow the urea concentrating power and phenolsulphonphthalein output, but not any approach to exact parallelism. The hourly excretions of potassium and sodium during the de Wesselow test were followed in two nephritic patients. One (R. G.) had a maximal dropsical tendency, the other (R. V.) a moderate one. During the salt-free dietary periods, administration of potassium chloride in the de Wesselow test decreased the sodium output in both patients. During the salt-containing dietary periods the de Wesselow test caused the more edematous patient to retain sodium and the less edematous one to lose it. In both patients the chloride concentration of the urine depended much more on the daily intake of sodium chloride than on the potassium chloride given in connection with the test.

AUTHOR'S SUMMARY.

THE SURFACE TENSION OF THE BLOOD SERUM IN NEPHRITIS. LOUIS LEITER, J. Clin. Investigation **3**:267, 1926.

In three cases of apparently pure lipoid nephrosis, the surface tension of the serum was abnormally low. In the patients with other types of nephritis it varied without apparent relation to the tendency to edema or to any other observed factor. Tendency to noncardiac edema in nephritis was found associated regularly with lowered plasma albumin content, but only irregularly with lowered serum surface tension.

AUTHOR'S SUMMARY.

PRECIPITATION PHENOMENA AND THE WASSERMANN REACTION. C. G. L. WOLF and E. K. RIDEAL, J. Hyg. **25**:366, 1926.

"Antigens" of varying sensitivity may be prepared by coating a dispersion of gum benzoin with saponin. When suitable dispersions so prepared are used, a zone of precipitation is observed which is more extended for specific than for normal serums. Differentiation is more pronounced as the region of

the isoelectric point of the globulin is approached. Precipitation is effected by the ions of salts present in the solution discharging the negative antigen suspension which has been sensitized by the protein of the serum. The mechanism of sensitization is described. Both albumins and globulins can protect or sensitize gum benzoin suspensions, the effect depending on an appropriate dilution. This effect occurs qualitatively irrespective of the hydrogen ion concentration of the medium. Quantitatively the position of the zone of precipitation and its extent is contingent on the reaction of the medium. The euglobulin fractions of normal and of syphilitic serums deprived as far as possible of their lipoids can be differentiated both by the Wassermann test and by precipitation tests. Delipoided euglobulins from horse serum will yield a Wassermann positive reaction when used in certain concentrations. In more concentrated solutions an anticomplementary effect is exhibited. Evidence is presented for the view that the euglobulins of specific serums differ rather in their composition or state of aggregation than in quantity from the euglobulin of nonspecific serums. The changes in sensitizing power and in the Wassermann reactivity of euglobulin caused by repeated freezing or exposure to ultraviolet rays run a parallel course. Attempts to change the Wassermann properties of normal serums are briefly described.

AUTHORS' SUMMARY.

SYNTHETICALLY PRODUCED SUBSTANCES WITH INSULIN-LIKE ACTION ON THE NORMAL AND DIABETIC ORGANISM. E. FRANK, M. NOTHMANN and A. WAGNER, Klin. Wchnschr. **5**:2100, 1926.

Synthalin is a synthetically prepared substance which may be amino-alkylineguanidine. The exact formula and method of preparation are kept secret. Given orally or subcutaneously to animals synthalin causes hypoglycemia and convulsions, and in depancreatized dogs it depresses the blood sugar. After the intra-arterial injection of synthalin, the blood sugar level of the peripheral venous blood is below that of the arterial blood. Each milligram of synthalin causes 1.2 Gm. of sugar to disappear from the urine of diabetic patients; the blood sugar falls below the renal threshold, acidosis ceases and other diabetic symptoms disappear. Insulin refractory patients respond to synthalin. Its action when given by mouth is slower and more prolonged than that of insulin. It is not toxic in the dosages given.

J. D. WILLEMS.

THE LACTIC ACID CONTENT OF PATHOLOGIC FLUIDS. R. SCHELLER, München. med. Wchnschr. **73**:1879, 1926.

The lactic acid and sugar content of pleural transudates is the same as that of the blood. The former is greatly increased, the latter absent, in the pleural exudates of tuberculosis and malignant tumors. Ascitic exudates of malignant tumors contain large quantities of lactic acid without reduction in their sugar content. In leukocyte-free fluids glycolysis does not occur for twelve hours during incubation.

J. D. WILLEMS.

SYNTHETIC MENTHOL. F. FLURY and H. SEEL, München. med. Wchnschr. **73**:2011, 1926.

Synthetic crystalline menthol with a freezing point of 35 C. has practically the same pharmacologic actions as natural menthol on mice, rats, cats and frogs, but it is less toxic. Several isomers differ considerably.

J. D. WILLEMS.

REACTION OF BLOOD IN EPILEPSY: COLORIMETRIC METHOD OF ESTIMATING p_H OF PLASMA. J. MARSACK and G. THACKER, Brit. J. Exper. Path. **7**:265, 1926.

The hydrogen ion concentration of the venous blood in epilepsy lies within the normal range.

THE PHOSPHATE AND CALCIUM MECHANISMS IN SKELETAL MUSCLE AFTER PARATHYROIDECTOMY. JAMES S. LOUGHRIDGE, Brit. J. Exper. Path. **7**:302, 1926.

The alterations in the hexose-phosphate mechanism in tetania parathyropriva are said by Loughridge to be secondary to the fatigue produced by the increased muscular movements occurring in this condition. The calcium content of the muscle is lowered in tetany, following parathyroidectomy.

AUTHOR'S SUMMARY.

Microbiology and Parasitology

THE POSSIBILITY OF HUMAN INFECTION AND INTOXICATION BY CERTAIN ORGANISMS OF THE SALMONELLA GROUP. S. R. DAMON and L. W. LEITER, Am. J. Hyg. **7**:27, 1927.

Bacillus suipestifer, Bacillus pestis-caviae, Bacillus sanguinarium and Bacillus anatum have been shown to multiply readily in all types of foods except those which have a strong initial acidity. These organisms grow readily in foods at body temperature and at room temperature. Growth of the organisms is but slightly retarded at icebox temperature. Multiplication of the organisms in food under any conditions offers such slight evidence of infection as readily to be overlooked. Prevention of food poisoning by the organisms must therefore depend on selection of raw products of unquestioned sanitary quality, care in the processes of preparation, so as to obviate contamination, and finally, preservation under such conditions as will assure a minimum of growth in case the food has been contaminated.

AUTHORS' SUMMARY.

THE PERSISTENCE OF STREPTOCOCCUS SCARLATINAE IN THE THROAT OF CONVALESCENT SCARLET FEVER PATIENTS. EDITH E. NICHOLLS, Am. J. Hyg. **7**:84, 1927.

Patients convalescent from scarlet fever are still infectious three weeks after onset of the disease.

EXPERIMENTAL ASPIRATORY ABSCESS. D. T. SMITH, Arch. Surg. **14**:231, 1927.

In 20 per cent of the animals used, guinea-pigs, mice, rabbits and dogs, lung abscesses were produced by intratracheal inoculation of material scraped from the alveolar border of teeth of patients with pyorrhea. The same organisms were recovered from the experimental abscesses and from nonoperative and postoperative abscesses in man.

N. ENZER.

THE INFECTIVITY AND VIRULENCE OF A FILTRABLE PHASE IN THE LIFE HISTORY OF B. FUSIFORMIS AND RELATED ORGANISMS. R. R. MELLON, J. Bact. **12**:279, 1926.

The aerobic modification of *Bacillus fusiformis* is a diphtheroid the granules of which pass a Berkefeld N candle and resist attempts at artificial cultivation. The granule-containing filtrate may represent a preparation of a "filtrable," virulent form of the organism.

ARTHUR LOCKE.

STUDIES IN SCARLET FEVER: I. THE AMOUNT OF SCARLATINAL TOXIN IN THE BLOOD OF PATIENTS WITH SCARLET FEVER. JAMES D. TRASK, J. Clin. Investigation **3**:391, 1926.

II. THE RELATION OF THE SPECIFIC TOXEMIA OF SCARLET FEVER TO THE COURSE OF THE DISEASE. FRANCIS G. BLAKE and JAMES D. TRASK, ibid., p. 397.

III. INFECTIONS WITH STREPTOCOCCUS SCARLATINAE IN PERSONS WITH SCARLATINAL ANTITOXIC IMMUNITY. EDITH E. NICHOLLS, ibid., p. 411.

IV. POSTSCARLATINAL IMMUNITY IN PATIENTS TREATED WITH ANTITOXIN. J. A. V. DAVIES, ibid., p. 423.

I. The amount of scarlet fever toxin found in the blood of scarlet fever patients during the acute stage of the disease varies between wide limits. The size and intensity of the local reaction caused by 0.3 cc of serum from scarlet fever patients in the skin of susceptible persons provides a rough but fairly satisfactory measure of the amount of toxin in the serum. Clinical estimation of the degree of toxemia in individual patients with scarlet fever is subject to a considerable error. Because of the difficulty of estimating the actual degree of toxemia by clinical observation, a generous excess of antitoxin should be used in the treatment of scarlet fever if the best results are to be obtained.

II. The specific toxemia of scarlet fever is a self-limited phase of the disease. The duration of the specific toxemia of scarlet fever parallels the duration of the rash. The degree of specific toxemia of scarlet fever, while the rash is present, depends largely on the presence and severity of septic complications. When the rash has faded the specific toxemia of scarlet fever is of low degree or has terminated, even though severe septic complications continue.

III. *Streptococcus scarlatinae* infections without clinical scarlet fever occur with considerable frequency among persons exposed to scarlet fever. The failure of persons infected with *Streptococcus scarlatinae* to develop clinical scarlet fever is probably dependent on the possession of immunity to scarlet fever toxin prior to the onset of the infection. Immunity to the toxin of *Streptococcus scarlatinae* as determined by the Dick test, does not necessarily provide the immunity to local pyogenic infections with *Streptococcus scarlatinae*.

IV. The degree of late immunity to scarlet fever developed by patients treated with adequate therapeutic doses of scarlet fever antitoxin during the toxemic stage of the disease appears to be less than that developed by patients who did not receive antitoxin. A correlation exists between the results of the skin tests of immunity to scarlet fever and the antitoxin content of the serum, whether the amount of serum antitoxin be determined by blanching or by neutralization experiments.

STUDIES CONCERNING THE RELATIONSHIP BETWEEN PNEUMOCOCCI AND STREPTOCOCCI. HOBART A. REIMANN, J. Exper. Med. **45**:1, 1927.

Morgenroth and his collaborators grew pneumococci in a medium containing optochin and derived variant forms of bacteria therefrom which were considered to be streptococci of the viridans group. We have repeated these experiments and have also derived variant forms. These atypical races, however, we have found to be identical with the R form of pneumococci which have been obtained

by various other methods. That these R cultures are still pneumocci and do not belong in the *Streptococcus viridans* group is supported by the following observations:

1. These strains are not bile-insoluble, but are more resistant to the lytic action of this agent than are type-specific pneumococci.

2. R strains behave like pneumococci and not like streptococci in the readiness with which cultures spontaneously autolyze and saline suspensions disintegrate during freezing and thawing.

3. Immunologic reactions of the variant pneumococci derived by Morgenroth's method are identical with the immunologic reactions of R forms of pneumococci derived by various other means.

The observations of Morgenroth and his associates in regard to the transformation of *Streptococcus haemolyticus* into *Streptococcus viridans* by treatment with rivanol could not be repeated in this laboratory. Explanation is not at hand for our failure to produce the change. It is, of course, possible that the twenty-six strains tested did not have suitable tendencies to variation or that the technic or reagents employed varied from those of Morgenroth.

AUTHOR'S SUMMARY.

EFFECT OF REPEATED FREEZING (—185° C.) AND THAWING ON COLON BACILLI, VIRUS III, VACCINE VIRUS, HERPES VIRUS, BACTERIOPHAGE, COMPLEMENT, AND TRYPSIN. T. M. RIVERS, J. Exper. Med. **45**:11, 1927.

Colon bacilli, virus III, vaccine virus, herpes virus, bacteriophage, complement and trypsin are either killed or inactivated by repeated freezing (—185 C.) and thawing. As might be expected, some of the agents are more resistant than others.

Hence it may be concluded that destruction or inactivation of an active agent by repeated freezing (—185 C.) and thawing is not proof that it was possessed of life.

AUTHOR'S SUMMARY.

STUDIES ON BACTERIAL ENZYMES. JAMES M. NEILL and E. L. GASPARI, J. Exper. Med. **45**:151 and 162, 1927.

Meningococci possess endocellular maltase, and also peptonase. The pneumococcus cells contain lactase and maltase.

THE ETIOLOGY OF VERRUGA PERUANA. HIDEYO NOGUCHI, J. Exper. Med. **45**:175, 1927.

The data obtained justify the conclusion that verruga peruana is caused by *Bartonella bacilliformis*. They also definitely establish the fact that the inoculation of blood of sanguineous exudate from lesions of verruga peruana is capable of inducing in susceptible persons a severe febrile systemic infection, such as that to which Carrion succumbed. The designation "Carrion's disease" is therefore the appropriate one for both forms of the infection. *Bartonella bacilliformis* may be regarded as a bacterium, since it has the essential features of that group of micro-organisms.

AUTHOR'S SUMMARY.

THE EFFECT OF p_H ON THE GERMICIDAL ACTION OF SOAPS. A. H. EGGERTH, J. General Physiol. **10**:147, 1926.

In working with potassium soaps prepared from a considerable ascending series of fatty acids, and using streptococcus, *Bacillus diphtheriae*, staphylococcus,

Bacillus typhosus and the cholera vibrio as test organisms, it was found that the lower members of the series were most actively germicidal in acid solution, the higher, in alkaline. This effect is ascribed to the action of p_H on dissociation residue and on solubility. The former may act in several ways: by modification of surface tension, of penetration into bacteria or of the partition coefficient between bacteria and water.

H. E. Eggers.

Studies in Microbic Heredity. R. R. Mellon and E. L. Jost, J. Immunol. **12**:331, 1926.

In addition to the well recognized serum factor (inhibitory substances) in the inagglutinability of freshly isolated strains, there is an unrecognized hereditary alteration in the bacterium itself which is the primary factor. This hereditary alteration involves reorganizations in the life cycle of the organism which are suggestively sexual in character. Through this mechanism inagglutinable or partially agglutinable types may be dissociated from agglutinable types or vice versa. These changes were observed in single cell cultures entirely independent of immune serums or exudates. Clearcut delineation between purely metabolic or physicochemical factors and the genetic factor was exemplified in changes of agglutinability which occurred in a single strain. When the cataphoresis technic is employed it appears that strains are inagglutinable because of a differential or binding capacity between specific agglutinin and the serum inhibitory factor, in favor of the latter. When a sensitization technic of 20 degrees is used this differential is partly compensated with a corresponding loss of the inagglutinability. Inagglutinable typhoid strains may vary markedly among themselves.

Authors' Summary.

Studies in Microbic Heredity. R. R. Mellon, J. Immunol. **12**:355, 1926.

The agglutinin-absorption test while undoubtedly of much value in the identification of organisms cannot be employed as a categorical criterion of genetic relationship in variation experiments. With certain groups the test is so highly specific that organisms having much in common otherwise may, on the basis of this test alone, be assumed to be quite different. On the other hand, organisms quite different morphologically or in other important aspects may be practically indistinguishable by the agglutinin-absorption test. The fact that reversible phases in the life history of an organism are not of necessity identical antigenically serves to correlate serologic heterogeneity with a truly pleomorphic life cycle. When one of these phases is dissociated out of the pleomorphic cycle as a stabilized morphologic type or variant the latter may not be antigenically identical with the parent organism. Differences in antigenic constitution appear to arise genetically by the same general botanic mechanism that modifies other genetic characters. These modifications arise in specialized developmental stages in the life history of the organism — in the endospores of the sporing bacilli, in the zygospores (or their reorganization equivalent) of the nonsporing bacilli and in the arthrospores, so called, of the cocci. Although they bear distinctive names and possess individual differences these three specialized stages appear to be fundamentally similar in a large botanic way. Such fundamental integrations promise to clarify, at the same time as they modify, many points in both practical and purely scientific bacteriology.

Author's Summary.

BACTERIAL VARIATION. P. R. EDWARDS and L. F. RETTGER, J. Immunol. **12**:377, 1926.

There are two antigens in the Salmonella group: One is specific to types within the group. The other relates the type with the group, and it is due to this that marked cross reactions between the different types occur. The two types of bacilli may be separated by plating stock cultures. When maintained under ordinary laboratory conditions the two types tend to resume the characters of the parent strains. The time required for this change to take place varies from a few days to several months. When subjected to unfavorable conditions strains may temporarily lose the ability to absorb agglutinins to which they have previously given rise. Strains may for a time lose their ability to agglutinate with group antiserum. It appears that the two antigens present in the para-B-suipestifer group are rather complex, and may at times be strain specific rather than type specific or group specific.

S. A. LEVINSON.

ULTRAMICROSCOPIC VIRUSES: I. CELL INCLUSIONS ASSOCIATED WITH CERTAIN ULTRAMICROSCOPIC DISEASES. G. M. FINDLAY and R. J. LUDFORD, Brit. J. Exper. Path. **7**:223, 1926.

A review is given in pictographic form of the voluminous literature on the intracellular inclusions associated with twenty-two diseases due to ultramicroscopic viruses: variola and vaccinia, sheep-pox, fowl-pox, scarlet fever, molluscum contagiosum, trachoma, rabies, distemper, varicella, herpes, meningoencephalomyelitis of horses, virus III infection of rabbits, paravaccinia, infections of unknown etiology, virus from guinea-pigs, foot and mouth disease, warts, polyhedral and other ultravirus diseases of insects, fowl plague, swine fever, African horse sickness and a disease of fowls.

ULTRAMICROSCOPIC VIRUSES: II. CYTOLOGY OF FOWL-POX. G. M. FINDLAY and R. J. LUDFORD, Brit. J. Exper. Path. **7**:256, 1926.

Fowl-pox has also been described as epithelioma contagiosum and molluscum. Ludford and Findlay contend that both these terms are misnomers, for the disease has nothing in common either with the epithelioma or with molluscum contagiosum in man. On the other hand, there is considerable evidence to show that the virus of fowl-pox, if not identical, is at least related to the virus of vaccinia. From the cytologic point of view, interest has largely centered in the curious cell inclusions found in the infected epidermal cells in this disease. They were first described as gregarine parasites, and since then have been the subject of many investigations. Up to the present, however, attempts to study the origin and nature of these inclusions by modern cytologic methods have not been made. The strain of virus used in the present investigation was obtained from a spontaneous epidemic of fowl-pox. The virus has been maintained for more than a year, under laboratory conditions, on the scarified skin of chickens from 1 to 2 weeks old, a fresh passage having been made every ten to fourteen days.

PATHS OF RENAL INFECTION. C. H. KELLAWAY, C. J. O. BROWN and F. ELEANOR WILLIAMS, Brit. J. Exper. Path. **7**:337, 1926.

In the guinea-pig, when the urethra is partially obstructed or the nervous mechanism of micturition disorganized, the introduction of pathogenic organisms into the bladder is followed within from two to three hours by the ascent of

the organisms into the pelvis of the kidney. This ascent can also be demonstrated by means of carmine particles. It occurs too rapidly to be accounted for by blood infection, nor is there any evidence that it takes place by way of the lymphatics of the ureter. In rabbits and cats, ascent along the lumen of the ureter is much more difficult to demonstrate and is of infrequent occurrence.

AUTHORS' SUMMARY.

THE VIRULENCE TESTING OF THE DIPHTHERIA BACILLUS AND ITS PRACTICAL APPLICATION. C. C. OKELL and H. J. PARISH, J. Hyg. **25**:355, 1926.

The authors recommend that the virulence of "morphological diphtheria bacilli" be tested by the intradermic injection of a preparation into guinea-pigs.

ARTHUR LOCKE.

SEDIMENTATION RATE IN PULMONARY TUBERCULOSIS. FREDERICK R. G. HEAF, Tubercle **8**:97, 1926.

The sedimentation rate of the blood was determined in 150 patients; the tube used was graduated in 200 divisions, with a total length of 1.25 cc. and a bore of sufficient diameter to prevent adherence of the red blood cells, which might affect the sedimentation rate. The method does not possess any value for the diagnosis or determination of activity of the disease in tuberculosis. Normal persons revealed a slope of the sedimentation curve (rate of sedimentation) greater in women than in men. The limit of sedimentation was reached the more rapidly the steeper the slope of the curve. In most normal curves a lag was noted during the first hour. A slight increase in the rate occurred according to age. In unfavorably progressing cases the curve approached a right angle at a rapid rate during the first hour, with completion of the curve between the third and fifth hour. Little difference was noted between the curves of males and those of females. In patients who are improving the curve approaches normal and the limit of sedimentation is not attained for from ten to fifteen hours. The prognosis was made correctly by the sedimentation test in 82 per cent of the 150 cases.

H. J. CORPER.

THE CHEMICAL NATURE OF THE ACTIVE PRINCIPLE OF TUBERCULIN. ESMOND R. LONG and FLORENCE B. SEIBERT, Tubercle **8**:111, 1926.

Chemical evidence is presented that the activity of tuberculin prepared on nonprotein synthetic mediums is associated with a protein substance. Any means tried was not successful in separating a nonprotein fraction with tuberculin activity. The persistence of activity on mild hydrolysis with beginning protein disintegration supports the view of activity being a function of a certain group of the protein molecule. Since with further hydrolysis of protein, activity disappears, it is unlikely that an active group can be split off, free from the rest of the protein.

H. J. CORPER.

EXPERIMENTAL RESEARCH ON THE VIRUS OF HERPES. M. LE FÈVRE DE ARRIC, Arch. internat. d. med. exper. **2**:835, 1926.

The author isolated a virus from a case of herpes which involved chiefly the lips, and inoculated it into rabbits. The inoculation was made usually by the subarachnoid route, but he also used epidermal, intracutaneous, subcu-

taneous, corneal and intratesticular inoculations. The rabbits developed the syndrome of encephalitis characterized by violent convulsions which dominated the picture and to which previous authors had drawn attention, and in addition to this, characteristic symptom complexes of the digestive, respiratory, circulatory and genito-urinary systems occurred. In the case of inoculation into the cornea there was occasional preliminary fever before the onset of symptoms. The blood showed marked leukocytosis with lymphocytopenia and secondary mononucleosis. The urine constantly contained albumin, occasionally casts and phosphates. The cell count of the spinal fluid was high, and four fifths of the cells were lymphocytes. Of the rabbits in which injections were performed by the subarachnoid route about 80 per cent developed the disease within three days, whereas the average duration of time before the onset of symptoms in inoculation of the cornea was from seven to eight days, of the testicle from nine to eleven days, and of the skin from fifteen to twenty days. There were two types of histologic lesions. One was an inflammatory type in which there was intense hyperemia of the meninges with interstitial hemorrhages. This was associated with an irregularly distributed meningeal exudate consisting chiefly of lymphocytes. Marked perivascular infiltration also occurred. In the other type there was rapid degeneration of the neuron, with karyolysis and marked neuronophagia. These lesions were the same as those described in encephalitis, but they were much more acute. They occurred throughout the brain, but to a much less extent in the medulla and cord. Similar lesions were found in the ganglia of the vagus and in the superior cervical sympathetic ganglion. Cellular inclusions, the origin of which was obscure, were found in the ganglion cells. Curiously enough, injection in the subcutaneous tissue gave negative results. It was difficult to isolate a virus in cases of human encephalitis, and in six cases of encephalitis and ten of a pseudo parkinsonian postencephalitic syndrome, the author was unable to obtain an encephalitic virus. He was also unable to recover the virus of Levaditi or his own herpes virus from inoculations of the fluid or material from human encephalitic cases. He concludes that the virus of herpes presents all the biologic characteristics of the virus said to cause encephalitis. Certain of the viruses of herpes are clearly possessed of an affinity for the central nervous system of the rabbit and in that respect are encephalitic. It is difficult to obtain a virus from a case of human encephalitis which will produce encephalitis in a rabbit.

N. Enzer.

Action of Radium in the Field of Biology. R. Bruynoghe, Arch. internat. d. med. exper. **2**:801, 1926.

The author studied the action of radium and radium emanations on the growth and virulence of bacteria, parasites, viruses, ferments and toxins. He found that radium emanations exercise a germicidal action, affecting microbes and spores to the same degree. He was not able to render the organisms resistant or to establish just what the changes in the cultures or the virulence of the microbes were. Apparently, the main effect which results from the influence of radiation is that although organisms are able to divide and retain their motility, they lose the power of being propagated in subcultures. Organisms rendered sterile by radium will not produce bacteriophage in culture. Parasites react in much the same manner; viz., they preserve their motility but lose their power of infectivity. The last is to be attributed to a disturbance of the function of division and not to diminution of their virulence. All the viruses examined, namely, rabies, encephalitis, herpes and the virus of vaccinia,

show the same sensitiveness; that is, they lose their power of infectivity and this was found to be especially characteristic of the neurotropic viruses. Bacteriophages were found to resist the action of radium. Radium did not affect the ferments. Toxins were little altered. Of the various antibodies only precipitins and hemagglutinins were damaged.

N. Enzer.

Primary Complex and Endocrine System. J. Kerner, Beitr. z. Klin. d. Tuberk. **64**:572, 1926.

In 112 cases of pulmonary tuberculosis in which autopsy was performed in the Institute for Tuberculosis Research in Yalta (Crimea) in 1925, only 34 per cent showed typical primary foci. This divergence from the results of other workers is explained by the fact that in the population of this country, the primary infection takes place frequently at a rather late date, and that it may sometimes develop into a progressive pulmonary tuberculosis without the intervention of a latent period. Processes of calcification and ossification are much influenced by the condition of the endocrine system. Particularly, the thymus gland greatly enhances calcification and osteoplastic processes. If the primary infection takes place after the activity of the thymus gland has ceased, calcification and ossification are much less likely to occur.

Max Pinner.

Some Cases of Pseudotuberculosis Aspergillina. H. Franke, Beitr. z. Klin. d. Tuberk. **64**:601, 1926.

In six penguins which died shortly after their arrival in a zoologic garden near Hamburg, the following pathologic changes were observed: The lower parts of the respiratory tract and the air sacs were studded with yellowish white hard nodules, approximately the size of a pinhead, some of which had coalesced and formed larger nodules. The walls of the air sacs were much thickened and partly adherent to each other. The inner surface of the air sacs frequently showed a grayish green moldy layer. The bacteriologic examination revealed the presence of *Aspergillus fumigatus* in all the lesions. The organism was pathogenic for both chickens and guinea-pigs.

Max Pinner.

The Blood Picture in Tuberculosis in High Altitudes. H. Scartazzini, Beitr. z. Klin. d. Tuberk. **64**:691, 1926.

In accordance with the observations of Knoll and Graf, two different types of erythropoetic reactions in high altitudes must be distinguished; in one type the erythrocytes are particularly increased, in the other type the increase of hemoglobin is predominant. The color index in type 1 approaches 1, in type 2 it sinks below 1. Type 1 is more frequent in the severer cases; type 2, particularly in grave cases, is prognostically a more favorable indication.

Max Pinner.

Concerning the Connections Between the Therapeutic Effect and the Reticulo-Endothelial Apparatus. I. L. Kritschewski and I. S. Meersohn, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:407, 1926.

White mice were infected with *Spirochaetae duttoni*, and the therapeutic effect of arsphenamine was tested. Splenectomy, together with "blocking" of the reticulo-endothelial system, impaired the therapeutic effect. Consequently,

the authors conclude that the effect of chemotherapeutic measures depends to a great extent on the condition of the reticulo-endothelial system.

PAUL R. CANNON.

THE VIRUS OF ENCEPHALITIS JAPONICA. I. TAKAKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:441, 1926.

The virus of encephalitis japonica, which is supposed to have caused the epidemic in Japan, in the summer of 1924, is pathogenic for rabbits, is filtrable and is transmissible from rabbit to rabbit. It appears to gain entrance through the nose and there remains latent for a time. Immune bodies can be demonstrated in the brain and blood, as well as in the serum of convalescent patients. The virus is not identical with the herpes virus.

In the second article, Takaki describes experiments contrasting the various encephalitis viruses, and showing that the virus of encephalitis japonica differs from the others studied.

PAUL R. CANNON.

TOXIC ALTERATIONS IN LEUKOCYTES IN TUBERCULOSIS. A. E. MAYER, Ztschr. f. Tuberk. **46**:337, 1926.

In tuberculosis, as in other infectious diseases, the leukocytes show toxic changes. Besides the shifting to the left in Arneth's blood formula one finds that either the nuclei of the neutrophils are more pyknotic, or they stain more feebly than normal; the chromatin structure is looser. Owing to the appearance of dark granules, the protoplasma assumes frequently a purple or grayish hue. Vacuoles are only infrequently observed. Anisocytosis of the neutrophils occurs. In the monocytes the granulation is diminished, and the nucleus is stained less dark; sometimes one finds lobated nuclei and vacuoles in the protoplasma. The rest of the white cells do not show any significant changes. All these alterations are not in any way specific for tuberculosis, and they do not always parallel the clinical course.

MAX PINNER.

ATTEMPTS TO ENHANCE THE VIRULENCE OF ACID-FAST SAPROPHYTES IN SCORBUTIC GUINEA-PIGS. W. VIETS, Ztschr. f. Tuberk. **46**:372, 1926.

Guinea-pigs rendered scorbutic by an avitamin diet were injected with various strains of acid-fast saprophytes. It was never possible to observe any tuberculogenic action of these saprophytes on the weakened organism of the guinea-pigs. The avitaminotic animals, infected or not, were frequently subject to spontaneous infection with pneumococci. The infected ones, and only these, acquired in addition to this frequent spontaneous infections with paratyphoid B, streptococci and gram-negative rods.

MAX PINNER.

A FURTHER COMMUNICATION ON TUBERCULOSIS IN INFANTS AND CHILDREN. A. GOHN and H. KUDLICH, Ztschr. f. Tuberk. **46**:391, 1926.

In the year 1925, autopsies were performed on forty-one children with definite tuberculous lesions in the Pathologic Institute of the German University in Prague. The ages ranged between 1½ months and 13 years. Thirty-eight had a primary pulmonary infection; in one case the portal of entrance could not be determined; one case had a primary focus in the middle ear (reported in a separate publication), and in one case the primary infection was in the region of the cervical lymph drainage. The distribution of the primary foci in

the lungs was much the same as that reported in earlier papers. In twelve cases the primary focus was caseated; in 5, caseated and softened; in 4 it was represented by a cavity with caseated masses; in 3, a fresh cavity; in 5, a smooth-walled cavity; in 1, a cavity with chalky contents; in 1, an encapsulated cavity, and in 1 a smooth-walled cavity with indurated wall. In 2 cases the primary focus was cheesy-chalky; in 1 case cheesy-chalky and encapsulated; in 1 case cheesy, softened and encapsulated; in 1 case cheesy and encapsulated; in 1 case cheesy and indurated, and in 1 case chalky. In infants signs of healing were not observed. The youngest patient who showed an anatomically healed focus was a girl, aged 1¼ years. All foci were located in the subpleural layers. Of the thirty-eight cases with primary pulmonary infection, thirty-four showed hematogenous propagation. Twenty-nine of the thirty-eight pulmonary cases showed macroscopically tuberculous changes in the lymph nodes of the bronchomediastinal lymph drainage, which extended to the venous angles.

MAX PINNER.

SANOCRYSIN IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS: I. TUBERCULOSIS OF RABBITS. T. MADSEN and J. R. MØRCH, Acta tuberc. Scandinav. **2**:99, 1926.

This appears to be the most extensive study published on sodium aurothiosulphate in experimental tuberculosis since Møllgaard's book on the subject. The following points are emphasized:

Most rabbits treated with the gold salt lose considerable weight during the treatment, and gain rapidly after the cessation of injections. Only temporary and slight loss of weight occurred in those animals which received antituberculous serum simultaneously with the sodium aurothiosulphate. Since even normal horse serum is noticably toxic for rabbits, the antiserum was prepared by injecting rabbits with "defatted" tubercle bacilli. This serum prevented regularly not only loss in weight, but, too, fatal toxic reactions which occurred not infrequently in animals that did not receive the serum.

The observation that the curative effect of the gold salt is negative if the treatment is begun simultaneously with the infection may be explained to indicate that "the action takes place indirectly and requires a certain state of reaction on the part of the body, in such a way that the action is only manifest, if a definite amount of tuberculous material is present." Animals injected with a bovine bacillus of low virulence were much more susceptible to the toxic action of sodium aurothiosulphate in the beginning of the treatment than rabbits injected with highly virulent organisms. The use of serum accordingly was not necessary in the treatment of the virulent infection. The observation that animals with a widespread tuberculous infection exhibit much less frequently any symptoms of "shock," contradicts the theory that attempts to explain this "shock" as gold poisoning only. Apparently the effects of low virulent infection can be cured with small doses of sodium aurothiosulphate; and the virulent and generalized infection, which requires much higher doses, tolerates a much larger amount of the drug without toxic reactions. The virulent infection treated with ten injections of 2 centigrams per kilogram of body weight, revealed the lungs of most of the animals (seven, respectively eight of ten) to be sterile three months after the infection; a lower dosage gave poorer results.

If one considers that the virulence of the infecting bacillus, the dosage of the gold salt and the interval between infection and treatment, are only some of the determining factors in the efficiency of the treatment, it will be readily

understood that the various workers obtained apparently conflicting results, and that the application to human cases requires much further study regarding dosage and indication. For medical application the most significant result of the present studies is the observation that acute and generalized infections require and tolerate more gold than chronic and localized ones.

MAX PINNER.

Immunology

A COMPARATIVE STUDY OF THE TOXICITY OF OX SERUM AND IMMUNE HETEROPHILE SERUM FOR THE GUINEA-PIG. ROSCOE R. HYDE, Am. J. Hyg. **7**:1, 1927.

The toxic agent in ox serum as it affects the guinea-pig is closely related to the complement content of the serum, since it follows the behavior of this agent. The toxic agent is not related to a known sensitizer of the serum. The toxicity of immune heterophile serums, on the other hand, is closely related to the sensitizer and is not related to the complement content of the serums.

AUTHOR'S SUMMARY.

QUANTITATIVE INTERDEPENDENCE OF SENSITIZER AND COMPLEMENT IN HEMOLYSIS. ROSCOE R. HYDE and ELIZABETH I. PARSONS, Am. J. Hyg. **7**:11, 1927.

Diagrams are presented to show the quantitative interdependence of sensitizer and complement as obtained under different experimental conditions.

CONCERNING D'HERELLE'S CLAIM THAT HUMAN SERUM MAY BE DIFFERENTIATED AS TO SEX BY ANAPHYLACTIC TESTS ON SENSITIZED GUINEA-PIGS. ROSCOE R. HYDE and ELIZABETH I. PARSONS, Am. J. Hyg. **7**:22, 1927.

In our experiments the human placental sensitized guinea-pig did not serve as a reliable guide in the determination of the sex origin of human serums.

AUTHORS' SUMMARY.

THE QUANTITY OF CHOLESTEROL IN THE BLOOD SERUM OF THE GUINEA-PIG AS AN INHERITED CHARACTER; ITS RELATION TO NATURAL RESISTANCE TO TUBERCULOSIS, AND TO TUBERCULOSIS INFECTION. RICHARD E. SHOPE, J. Exper. Med. **45**:59, 1927.

Infection with tubercle bacilli of bovine type did not produce any alteration in the serum cholesterol content in guinea-pigs. Certain controlled variations in diet did not produce any changes in the serum cholesterol content in guinea-pigs. Inbred families of guinea-pigs known to manifest differing resistances to tuberculosis gave differing serum cholesterol values, but direct relationship between the two sets of phenomena could not be established. It seems probable that in the guinea-pig the cholesterol content of the blood serum is influenced by inherited factors.

AUTHOR'S SUMMARY.

STUDIES ON THE OXIDATION AND REDUCTION OF IMMUNOLOGICAL SUBSTANCES. JAMES M. NEILL, J. Exper. Med. **45**:105, 1927.

Immunization with solutions of the intracellular substances of pneumococci, in which the hemotoxin has been rendered inactive by oxidation yields an antibody which neutralizes the active or reduced hemotoxin.

AUTHOR'S SUMMARY.

A Chemist's Homage to the Work of a Biologist. Henry E. Armstrong, J. General Physiol. **8**:653, 1927. (Jacques Loeb Memorial Volume.)

"I am old enough to look back to the revelation of the nature of communicable disease by Pasteur and Lister — to the close of the controversy over spontaneous generation — to the introduction and development of bacteriology as a separate discipline. During my early career, I taught in a medical school. Pasteur had no wide knowledge of chemistry — had he remained a chemist, he would undoubtedly have risen to his opportunities. Instead, he was carried away by such small things as the micro-organism and the silkworm. He became a biologist but in so doing carried over the precise method of chemistry into biology. His distinguishing characteristic was an intense logic — in everything he did, he was logical. He began as a geometrician: he saw things not in the flat or on paper but in the solid; he, therefore, had proportionate judgment. The scientific worker today too often has but a flat mind. Great use has been made of Pasteur's findings; our modern sanitary system [and preventive medicine] is built entirely upon the foundations he laid. On the biological side, there has been no new step taken equivalent to that originally taken by Pasteur himself. The reason is plain. No sufficient use is being made of chemistry. Those who approach from the medical side, as a rule, have no chemical experience worth calling experience. The chemist, on the average, tends to mathematics and physics rather than to physiology. In the course of my career, I have met very few chemists with any real biologic afflatus. The biological mind seems to be amathematical, as a rule; when it takes on mathematics, it suffers and is carried away by formulae. A reform of our system of preliminary medical training is urgently required — it has been long evident that medicine is but applied chemistry, yet this is in no way recognized, notwithstanding the example set by men like Gowland Hopkins and Loeb. It is only necessary to take a work, such as that on *Infection and Resistance* by Professor Hans Zinsser, to realize in what hopeless state of muddle and confusion the subject now is. The work that is being done in this field is, for the most part, wasted effort, because there is no clear thinking behind it — no logic — no proper sense of method — no defined attack. The future rests with chemistry and the crystalline; the interpretation of the colloid state being only possible through an understanding of the crystalline. This Loeb saw."

Effect of Variations of Salt Content of Blood on the Bactericidal Power. A. Fleming, Brit. J. Exper. Path. **7**:274, 1926.

Leukocytes only function efficiently within certain limits of salt concentration, and when the salt content falls below or rises above these limits, the leukocytes do not emigrate and do not take up or destroy bacteria. When a large amount of salt is injected into an animal, so that the salt content of the blood is materially raised, the normal bactericidal power is temporarily lost, but after a few hours it is greatly enhanced. When smaller doses are injected, the preliminary fall in the bactericidal power is avoided, but the subsequent rise is marked, and in man, the injection of an amount of salt so little that when diluted with the blood it would only increase the salt content by 0.01 per cent causes after three hours a great rise in the bactericidal power of the blood. The intravenous injection of hypertonic salt solution has been used in cholera and other diseases, with a view to increasing the blood volume, but the results detailed by Fleming show that such injections may produce benefit, not only by virtue of their fluid content, but also by conferring on the patient's blood greater powers of destroying the infecting bacteria.

OBSERVATIONS ON SIX ANOMALOUS BLOODS, WITH REFERENCE TO THE THEORY OF ISOAGGLUTINATION. S. C. DYKE, Brit. J. Exper. Path. **7**:294, 1926.

The observations point to the conclusion that in the absence of absorption tests, many bloods of group I will escape detection. This fact is of importance: (1) in that it offers an explanation of the apparent rarity of bloods of group I; (2) in its bearing on the matching of bloods for transfusion, and (3) in its medicolegal applications.

AUTHOR'S SUMMARY.

THE RETICULO-ENDOTHELIAL SYSTEM AND HAEMOLYSIN FORMATION. GEO. R. ROSS, Brit. J. Exper. Path. **7**:346, 1926.

Saturation of rabbits, by daily intraperitoneal injections of trypan blue for periods up to one month, did not have any effect on subsequent hemolysin formation in these animals, in response to intravenous injections of sheep red cells.

AUTHOR'S SUMMARY.

ON THE COMBINED ACTION OF ANTIGENS AND ANTIBODIES ON THE BACTERICIDAL POWER OF DEFIBRINATED BLOOD. E. W. TODD, Brit. J. Exper. Path. **7**:368, 1926.

The formation of precipitates in hemobactericidal tests is destructive to the bactericidal power of the blood. When the bactericidal power of blood which contains precipitin is tested on the homologous organism, precipitinogen is liberated by the growth of the organism in the blood, and the resultant precipitate reduces the bactericidal action of the blood. Thus, when the bactericidal power of a patient's blood is tested against staphylococci a low bactericidal value may be expected if, owing to past infection, inoculation or any other cause, the blood contains staphylococcal precipitin.

AUTHOR'S SUMMARY.

THE PRODUCTION OF TUBERCULOUS SKIN ALLERGY BY SIMULTANEOUS INOCULATION OF TUBERCULIN AND VARIOLA VACCINE (MORO UND KELLER). H. FERNBACH, Beitr. z. Klin. d. Tuberk. **64**:660, 1926.

The skin allergy against tuberculin which develops after the simultaneous injection of old tuberculin and variola vaccine can be elicited not only by tuberculin but by concentrated glycerolated broth as well. The same sensitiveness can be produced by a simultaneous injection of concentrated glycerolated broth and vaccine, which shows that the allergy produced is independent of the active principle in old tuberculin.

MAX PINNER.

ERRORS AND DANGERS IN THE DETERMINATION OF THE BLOOD GROUPS. P. SCHUMACHER and K. ATZERODT, Klin. Wchnschr. **5**:2016, 1926.

A severe shock followed the transfusion of a person of group I with 5 cc. of blood of group II.

Tumors

LYMPHOSARCOMATOSIS. BENJAMIN ROMAN, Bull. Buffalo Gen. Hosp. **4**:55, 1926.

The patient was a woman, aged 70, who during life exhibited the picture of a generalized hyperplasia of the lymphatic organs including great enlargement of the spleen. The leukocyte count was from 22,000 to 26,000 per cubic millimeter, 78 per cent of which were medium sized lymphocytes. The picture

at necropsy was difficult to interpret. Only Hodgkin's disease could be left out of consideration, as the growths were composed of uniformly small lymphocytes. While many of the features coincided with those of leukemia, the total absence of changes in the liver, extensive perirenal infiltration, and nodular invasion of the lungs and spleen spoke against it. The insignificant increase in the white blood cells and the mature character of the tumor cells prevented the identification of the process with leukosarcomatosis (Sternberg). On final analysis it seemed least objectionable to regard the case as one of lymphosarcomatosis.

AUTHOR'S SUMMARY.

MALIGNANT NEUROBLASTOMA. BENJAMIN ROMAN, Bull. Buffalo Gen. Hosp. **4**:58, 1926.

An infant, aged 9 days, with jaundice and an enlarged liver, at necropsy revealed a tumor limited to the suprarenals and the liver. The latter was diffusely involved, its parenchyma almost completely replaced, and its form preserved. Histologically the tumor showed the characteristic structure of a neuroblastoma, but nerve fibrils could not be demonstrated in it. The origin of the tumor was probably in the left suprarenal. The presence of icterus and the observation of bile in the gallbladder, in spite of almost total destruction of the liver cells, would lend support to the newer theories of bilirubin formation as based on hepatectomy experiments in dogs.

AUTHOR'S SUMMARY.

DIFFUSE CARCINOMATOSIS OF THE LUNGS. BENJAMIN ROMAN, Bull. Buffalo Gen. Hosp. **4**:58, 1926.

A laborer, aged 32, with symptoms referable to the stomach and embarrassed pulmonary circulation, showed diffuse, chiefly lymph vessel invasion of both lungs by a secondary carcinoma, the primary tumor being a small scirrhus of the stomach. The gross appearance of the lungs at necropsy was that of an interstitial pneumonia. Roentgenograms of the lungs taken during life and post mortem, and a photograph of a lung, are given for comparison.

AUTHOR'S SUMMARY.

GLUTATHIONE CONTENT OF NORMAL ANIMALS. J. W. THOMPSON and C. VOEGTLIN, J. Biol. Chem. **70**:793, 1926. GLUTATHIONE CONTENT OF TUMOR ANIMALS, Ibid., p. 801.

The tissues of the albino rat contain proportionately less glutathione as the age of the animal advances.

The necrotic portions of malignant, transplantable, mammalian tumors do not contain glutathione, although the peripheral, nonnecrotic portions may contain amounts of this substance as large as those which occur in liver tissue. The total glutathione content of the normal tissues decreases as the tumor grows larger, a relation that may have some bearing on the genesis of cancer cachexia.

ARTHUR LOCKE.

THE COMPARATIVE PATHOLOGY OF CANCER OF THE THYROID, WITH REPORT OF PRIMARY SPONTANEOUS TUMORS OF THE THYROID IN MICE AND IN A RAT. MAUD SLYE, H. F. HOLMES and H. G. WELLS, J. Cancer Research **10**:175, 1926.

In districts where goiter is common the occurrence of malignant tumors of the thyroid gland is frequent. This occurs possibly because the proliferative activity in simple goiter predisposes to the formation of malignancy. But few

cases of malignant diseases of the thyroid are found in lower animals, with the exception, however, of the dog, in which goiter is extremely common. In Chicago, for instance, it is difficult to find a normal thyroid in an adult dog. In spite of the frequency of spontaneous tumors in mice, the thyroid in this rodent, in extremely rare instances, is the seat of a primary tumor. In 51,700 autopsies on mice that yielded over 5,000 primary tumors in almost all parts of the body, only seventeen of the rodents found had noticeably enlarged thyroids, of which five were simple goiters, and twelve were malignant growths. The histology of the twelve tumors is given in detail. The authors admit great difficulties in the recognition of malignant thyroid growths in mice. In one wild rat they found three distinct spontaneous malignant tumors: an adenocarcinoma of both lobes of the thyroid; an adenocarcinoma of the intrahepatic bile ducts, and a hemorrhagic sarcoma of the liver. They believe that in the wild rat tumor is more frequent than commonly believed. "The infrequency of malignant growth in wild animals depends on the infrequency with which wild animals reach old age."

From the histologic point of view the malignant thyroid tumors found by the authors were of interest in that they showed a tendency to present a mixed type of structure.

In regard to age, the thyroid carcinomas occur within the usual age period for other forms of visceral carcinoma in mice.

The outstanding feature in the investigation is the fact that in a community in which men and dogs develop goiter frequently, mice are in only rare instances affected by the disease. This is due apparently to the fact that the thyroids of mice, of the stock investigated, are not under any such functional strain as human and dog thyroids appear to be.

B. M. Fried.

A Study of the Athreptic Theory of the Growth of Cancer. Kanematsu Sugiura and Stanley R. Benedict, J. Cancer Research **10**:194, 1926.

The purpose of Sugiura and Benedict's study was to secure further information bearing on Erlich's athreptic theory of the growth of cancer. The athreptic theory was based on experiments which showed that an actively growing transplanted mouse carcinoma or sarcoma prevented the growth of secondary implants in the majority of cases. Erlich explained this fact on the basis that special nutritive substances are required for the growth of neoplastic cells, and that these cells take up such food stuffs more rapidly than normal somatic cells. The limited amount of growth promoting substances is all taken up by the first implant, thus preventing the development of the second implant.

In their experiments Sugiura and Benedict used the albino rat, from 50 to 150 days old, and Flexner-Jobling rat carcinoma. Their conclusions are that the reinoculation is successful if it is made immediately after the primary implantation. At the end of the seventh day the animal is completely refractory to the second implant. This induced resistance, however, diminishes slowly after that point so that after the fourteenth day from the time of first tumor inoculation the animals again become suscepible to reinoculation. When the secondary implantations are made five days after the primary implantation, in many instances, not only did the second tumors fail to grow, but also the first implants disappeared. In the experiments growth of the secondary implants occurred almost always among the positive primary implants, and they were seldom found among the negative primary implants. It was also observed that sometimes retrogressing tumors were activated by the reinoculation of fresh tumor tissue.

B. M. Fried.

MALIGNANT TUMORS OF THE ADRENAL IN CHILDREN. P. A. BENDIXEN and F. H. LAMB, J. Lab. & Clin. Med. **12**:130, 1926.

Malignant tumor in suprarenal medulla is not unusual. In the majority of cases an orbital hemorrhage is the first sign observed, and it may occur before any tumor is palpable. The orbit first involved is often on the same side as the primary tumor. Diagnosis should not be difficult once the orbital hemorrhage has occurred; the disease is likely to be mistaken only for trauma, chloroma and scurvy. Metastases probably occur by way of the lymph stream; metastasis in the skin is rare. As the medulla of the suprarenal gland is neuroectodermic in origin, these malignant tumors are similar in their histologic structure to malignant neoplasms of the sympathetic nervous system, and may be designated as neuroblastoma.

S. A. LEVINSON.

INSULIN IN NORMAL AND CANCEROUS TISSUES. W. CRAMER, F. DICKENS and E. C. Dodds, Brit. J. Exper. Path. **7**:299, 1926.

Insulin is present in normal tissues in appreciable amounts. It is absent from malignant new growths. The cells of normal tissues oxidize glucose, the cells of malignant new growths split glucose, as Warburg found, with the formation of lactic acid. This parallelism suggests that the oxidation of glucose by the cells is dependent on the presence of insulin at the site of oxidation.

AUTHORS' SUMMARY.

THE SUSCEPTIBILITY OF THE INFECTIVE AGENT OF THE ROUS CHICKEN SARCOMA TO THE ACTION OF ULTRAVIOLET RAYS. S. L. BAKER and P. R. PEACOCK, Brit. J. Exper. Path. **7**:310, 1926.

Baker and Peacock worked out a technic for obtaining quantitative lethal effects on organisms with ultraviolet rays. Various types of bacteria were tested and showed little difference in susceptibility. The filtrate of Rous chicken sarcoma contained sufficient coagulable protein to absorb a considerable proportion of the bactericidal wave lengths. The necessary equation was made by suspending *B. coli* in a sample of the filtrate and finding the lethal dose under these conditions. Samples of the filtrate were irradiated and injected into the pectoral muscles of fowls. The results varied, but it was evident that some samples of the filtrate remained active, though attenuated, after a dose of rays equal to five times the lethal dose for *B. coli* in filtrate. It is suggested that the relative insusceptibility of the agent in the tumor filtrates is due to its small size.

F. CARPENTER.

THE ACTIVATION OF FILTRATES OF THE ROUS SARCOMA BY AN AGENT IN BROTH CULTURES OF JENSEN'S RAT SARCOMA. S. L. BAKER, Brit. J. Exper. Path. **7**:377, 1926.

It is shown that an agent is present in cultures of Jensen's rat sarcoma that will activate chloroformed filtrates of the Rous chicken sarcoma. 1. In two cases this agent has been demonstrated in a first and a second subculture. Further, an agent in primary cultures of the rat sarcoma will activate filtrate attenuated by dilution. Definite conclusions are not reached as to the nature of the activating agent in the cultures.

AUTHOR'S SUMMARY.

EARLY LOCAL AND GENERAL CHANGES IN TARRED ANIMALS WITH SPECIAL REFERENCE TO RETICULO-ENDOTHELIAL APPARATUS. BRUNO BORGHI, Tumori **12**: 271, 1926.

The author has studied the local as well as the general pathologic changes in rats and rabbits whose skin has been painted with coal tar. The tissues of

some of the animals had been vitally stained with trypan blue. He found fatty degeneration and focal necroses of the liver cells with early cirrhosis and ordinary degenerative changes in the kidneys. In the rats especially, the Kupffer cells were heavily infiltrated with tar. Locally, physicochemical changes in the connective tissue appear to precede invasion by the proliferating surface epithelium. Many histiocytes collect in the connective tissue at the point of application of the coal tar. The cells of the reticulo-endothelial system are damaged early in the process. Borghi thinks that the cells of this system may have an important function in maintaining the balance of the various tissues of the body and that if this defensive function is paralyzed the proliferating epithelium can more readily invade the connective tissue. His researches also show locally an early abolition of the sharp dividing line between epithelium and connective tissue.

W. Ophüls.

Experimental Neoplasms from Autotransplants of the Mucous Membrane of the Uterus. Giuseppe Dossena, Tumori **12**:291, 1926.

In connection with Sampson's theory of the implantation of uterine mucous membrane on the pelvic peritoneum, Dossena has repeated Jacobson's experiments on the artificial production of such implantation in animals. In his experiments Dossena used rabbits and white rats. He found that in these animals small pieces of the uterine mucous membrane obtained from the same animal can attach themselves at various points, even to the intestinal wall, and can develop into unilocular or plurilocular cysts, into adenomatous cysts or into papillomas and mixed forms. Even as late as 140 to 150 days after implantation the tissues are still in process of development and do not show the slightest evidence of regression.

W. Ophüls.

Recklinghausen's Disease. Giacomo Quarti, Tumori **12**:319, 1926.

The author reports the clinical history and the autopsy observations in a case of neurofibromatosis. He concludes that this disease is a condition of the connective tissue system caused by two factors: repeated attacks of infection and a natural predisposition. The vegative system seems to be concerned in its production acting through an endocrine disturbance.

W. Ophüls.

Carcinoma of the Small Intestines in Adolescents. P. L. Badile, Tumori **12**:355, 1926.

Badile reports a case of carcinoma of the small intestine in a boy, aged 15 years. The tumor had been removed surgically. The observation is of interest on account of the great rarity of this form of carcinoma especially in children, on account of the interesting symptom complex produced by it and on account of the complete success of the surgical treatment.

W. Ophüls.

Epithelial Tumors of the Cornea. L. Poleff, Klin. Wchnschr. **5**:2256, 1926.

Tumors of the cornea are histogenetically first epitheliomas and then through an intermediate form become either papillomas or carcinomas. Papillomas may later become malignant. The early recognition of the nature of the tumor is difficult.

J. D. Willems.

HISTOGENESIS OF STROMA OF EPITHELIOMA. KROMAYER, Ztschr. f. Krebsforsch. **24**:1, 1926.

Kromayer is convinced of the transformation of individual cells of the basal layer of the epidermis into connective tissue cells of the underlying stroma, a process which he terms desmoplasia. This characteristic of what he calls the "Parenchymhaut" (epidermis plus cutis vasculosa) he believes to hold also for the mucous membranes and all parenchymatous organs. The basal epithelial cells in any situation, therefore, serve as a reservoir which provides not only functioning epithelial cells but also stroma cells. He describes a similar process in epitheliomas of the skin and concludes that in these neoplasms growth is chiefly expansive rather than infiltrative, the apparently invaded stroma within the tumor parenchyma having come from epithelial cells of the latter.

O. T. SCHULTZ.

ROFFO'S NEUTRAL RED SERUM REACTION FOR CANCER. M. BERIĆ, Ztschr. f. Krebsforsch. **24**:10, 1926.

Roffo claimed specific diagnostic value for the color reaction which occurs when five drops of a 1 per cent solution of neutral red are added to 2 cc. of clear serum. In sixty-four cases of neoplasia he obtained a uniformly "positive" reaction (red), and in 114 cases of his nontumor group a uniformly "negative" reaction (yellow). Berić, repeated the "test" on thirty-five patients with malignant tumor, the reactions being "positive" in sixteen and "negative" in nineteen, and on sixty-four patients free from tumor, the reactions being "positive" in nineteen and "negative" in forty-six. The results warrant the author's conclusion that the reaction is not specific and that it is without diagnostic value.

O. T. SCHULTZ.

RESISTANCE IN DOUBLE TUMOR INOCULATIONS. W. CASPARI and E. SCHWARZ, Ztschr. f. Krebsforsch. **24**:15, 1926.

By means of double inoculations of tumor tissue into mice, the authors studied the mutual effect of the two inoculations on each other. In one series of experiments the first inoculation was made intravenously, the second subcutaneously. In another series both inoculations were made subcutaneously. The interval between inoculations varied from nine to 113 days. The tumors used were transplanted carcinoma, sarcoma and chondroma, various combinations of homologous and heterologous tumors being used in the double inoculations. Virulence, as applied to tumors, consists of two components which do not always run parallel. One is the proliferative capacity of the tumor tissue, a property which is measured by the rapidity of growth of the neoplasm and which is usually associated with early necrosis of the rapidly growing tumor tissue. The other is the inoculability of the tumor, which is measured by the percentage of successful "takes." The chondroma used by the authors yielded the largest number of successful inoculations but brought about a lesser degree of resistance to a second inoculation than did the carcinoma or sarcoma. The authors conclude that there is not a direct relationship between the virulence of a tumor and the resistance to a second inoculation. Any relationship that exists is indirect and depends on the proliferative capacity of the tumor tissue, which goes hand in hand with the necrotization of the tissue. Increased resistance is due to liberation from the necrotic tumor tissue of degradation products, which are termed necrohormones.

O. T. SCHULTZ.

SARCOMA OF A SPARROW. P. COHRS, Ztschr. f. Krebsforsch. **24**:33, 1926.

A brief report is given of a small round cell sarcoma, situated at the junction of the lower beak with the head, in the common sparrow, a species of bird in which neoplasia is said never to have been reported.

O. T. SCHULTZ.

ISAMINBLUE IN INOPERABLE MAMMARY CARCINOMA. R. ROOSEN, Ztschr. f. Krebsforsch. **24**:35, 1926.

Roosen claims that the dye isaminblue is nontoxic when injected intravenously and is taken up by the stroma of carcinomas. The deposition of the dye is associated with regression of the tumor. In a series of inoperable carcinomas of the mammary gland, the dye solution was injected directly into the tumor and into the surrounding tissues. From ten to fourteen days after the injection, when the skin has taken on a deep color, the neoplasm begins to regress, sometimes with such a degree of liquefaction that it is advisable to withdraw the liquefied material by means of a syringe. If lymph node metastases are present, the dye is injected also intravenously. Metastases in other tissues are not influenced by the material. The author does not make any claims for more than temporary improvement in the inoperable tumors treated by him.

O. T. SCHULTZ.

FREQUENCY OF MULTIPLE TUMORS. L. PUHR, Ztschr. f. Krebsforsch. **24**:38, 1926.

With the aim of determining the frequency of multiple tumors in the same person, Puhr analyzed the necropsy records of the II Pathological-Anatomical Institute of Budapest for the twenty-one years from 1903 to 1924. In a total of 6,718 necropsies, there were 1,559 (23.2 per cent) with one or more neoplasms. The latter were multiple in 219 cases, that is, in 3.25 per cent of all necropsies, and in 14.94 per cent of cases with tumor. The material is tabulated according to the occurrence in individual cases of two, three, four and five different tumors. There were two examples of two carcinomas, one of carcinoma associated with sarcoma, one of two carcinomas with a benign tumor and one of two carcinomas with two benign tumors. The largest single group was made up of cases in which carcinoma was associated with a single benign tumor (eighty cases), the next largest of the combination of two benign tumors (fifty-two cases). A criticism which may be made against the statistical analysis is the inclusion, among the benign tumors, of certain conditions of which the neoplastic character may be doubted; struma of the thyroid, hypertrophy of the prostate and cysts of the ovary and other organs. Developmental anomaly and a single tumor were associated in seven cases and anomaly and two tumors in seven cases. The most frequent anomaly was diverticulum of the intestine, chiefly Meckel's, which occurred in five of the fourteen cases. The author concludes that multiple tumors occur much more frequently than is usually believed to be the case. This conclusion must be modified by the statement that the simultaneous occurrence of two or more malignant tumors is rare even in his material. The frequency of multiple tumor involvement decreases proportionately with the number of different tumors in the same person. The frequency of the occurrence of multiple benign tumors, the origin of which may be ascribed to misplacement or other developmental error, leads to the conclusion that developmental factors are important in the pathogenesis of such neoplasms, and that congenital constitutional factors probably play a rôle also in the development of malignant tumors.

O. T. SCHULTZ.

Medicolegal Pathology

Is Epilepsy Made Worse by Injuries of the Head? C. Kurtz, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:260, 1926.

From an experience with 1,064 cases in a Berlin institution for epileptic patients, the records of only eighteen subjects were found suitable for this study. Of these, four patients died soon after injury, four had an increased frequency of epileptic convulsions and four others had a diminished frequency following injury of the head. The trauma of the head in the remaining six patients was apparently without influence on the subsequent course of the disease. Only instances of severe injury were considered. Extensive scalp wounds, unconsciousness and bleeding from the nose and from one or both ears were common symptoms.

Since authorities have differed widely, some vigorously supporting a benign influence and others with corresponding assurance stating that epilepsy is aggravated by grave injuries of the head such as epileptic patients frequently sustain, the inconclusiveness of the evidence presented by Kurtz has a real medicolegal value. The suggestion is made that when betterment or cure follow such injuries or the various operations on the head employed for epilepsy, such results are due to an improved blood supply for the brain.

E. R. Le Count.

Arsenic in the Ash of Cremated Bodies. H. Jesser, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:275, 1926.

In the ash of each of nine bodies, marked traces of arsenic were found when their cremation, one after another, was preceded by that of a body into which 1 Gm. of arsenious acid had been injected. Difficulty of thoroughly cleaning the compartment in the furnace where the bodies were burned, and repeated volatilization of the arsenic so that it became a constituent of the ash in subsequent cremations, are offered as explanations.

E. R. Le Count.

An Unusual Bullet-Wound of Entrance of the Cranium. S. Talwik, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:279, 1926.

From a pendulum-like swinging on its long axis attributed to passing through head covering, the bullet fired through the right parietal bone (suicide) made an opening 24 mm. long by from 7 to 9 mm. wide, shaped like the bullet. The square rear end of the bullet was swinging outward as it passed through the bone and at that end the margin of the hole was bevelled outward like a wound of exit. At the other end, more of the inner table had been shot away, so that the bevelling was that commonly encountered in entrance wounds.

Added support for this explanation for the peculiar characteristics of the wound in the bone was afforded by three fractures with the greater gapping in the outer table and other evidence of their production by force exerted from within the cranium. These fractures were the only ones present and they radiated out from the end of the oblong hole where the square end of the bullet swinging out had splintered away more of the outer table. There was no exit wound and the bullet was found in the brain. E. R. Le Count.

ELECTROCUTION WOUNDS OF THE HEAD. ELIZABETH GUBLER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:406, 1926.

A good account is given of the injuries of the head of one body where the current entered, and a good summary from the literature of those in eleven other bodies. In eight of the twelve cases in which the scalp was burned or burned and torn, there was necrosis of the underlying bone. The bone was brittle, blanched or slightly discolored by burning, or there was a defect in the bone from calcination. In two bodies small pearl-like crystals of calcium phosphate incrusted the necrotic bone. The dura underneath such wounds was usually intact, in some heads it was slightly browned and in one the dura forming the floor of the open wound had in it small sievelike perforations.

Gross changes of the brain are either slight or altogether absent. Of the brains in these twelve wounded heads, that studied by Gubler is apparently the only one examined microscopically. The minute changes found by her were insignificant. Mentality is not, as a rule, impaired when persons are resuscitated by artificial respiration from the unconsciousness and shock caused by electricity.

E. R. LE COUNT.

REMOVAL OF THE COLON LINING; SELFMUTILATION. J. LOESSEL and J. JAKI, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:419, 1926.

A woman, aged 18, with dementia praecox wounded herself during the night in the perineum and the next morning was found in a pool of blood with about 1 meter of the lining of the colon projecting from the wound. The wound continued into the back wall of the vagina and the front wall of the rectum. It is assumed that she succeeded in pulling on the mucosa of the rectum which prolapsed into the wound and gradually drew out the mucosa and submucosa as a tube from the colon as far as the hepatic flexure.

There was a chronic inflammation of the colon which, by loosening the layers, had made the mutilation possible. It was not possible to repeat such a stripping away of the two inner coats using the healthy colons of dead bodies. The patient died six hours after operation, and a necropsy was performed. The article does not contain any suggestion regarding what caused the colitis.

E. R. LE COUNT.

PRIORITY OF CRANIAL FRACTURES. K. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:430, 1926.

It was found possible by study of the skull of a body exhumed six years after murder by two men, to determine which of two injuries was made first. One man had first crushed the back of the head with a weapon and the other then fired a bullet through the head. The bullet passed through from the front and out at the back where the bones had previously been extensively comminuted.

E. R. LE COUNT.

SUICIDAL STAB WOUND OF THE BACK. W. MUNCK, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:436, 1926.

The direction, depth and other peculiarities of four incised and two stab wounds of the front of the neck, of superficial wounds of each wrist, of a stab wound of the front and of another of the back of the trunk were all in accord with attempted suicide. That of the back was at the level of the eleventh and twelfth ribs, slightly to the left and in one of the few locations

in which a penetrating wound of the thorax can readily be self-inflicted with the right hand. None of the wounds was fatal and death was by drowning. The report is made because of a failure to find records in the literature of suicidal stab wounds of the back.

E. R. Le Count.

Veronal Poisoning and Veronal Excretion. F. Reiche, Klin. Wchnschr. **5**:2112, 1926.

A heavily insured patient with pneumonia died in protracted coma, during which veronal was found in the urine. To settle a question of suicide, attempts were made to establish the quantity of veronal taken from the quantity excreted in the urine. The results with nineteen patients treated experimentally varied so greatly that a reliable conclusion was not reached.

J. D. Willems.

Technical

A New Method of Gastric Analysis. A. M. Altshuler, Ann. Clin. Med. **5**:464, 1926.

Altshuler investigated the Zimnitzky method for determining the secretory function of the stomach, which is based on repeated physiologic stimulation with beef broth. A test breakfast of 200 cc. of warm beef broth (400 Gm. of lean beef in 1 liter of water) is given. At fifteen minute intervals during the following hour, 10 cc. of the stomach contents are aspirated. At the end of one hour, the stomach is emptied and the procedure is repeated for another hour. Each aspirated sample is tested at once for mucus, bile, free hydrochloric acid, total acidity, lactic acid and occult blood. Altshuler grouped his patients into five types: (1) the normal type, in which the acidity for the second hour is greater than that of the first; (2) the asthenic type, in which the total figures for the first hour exceed those of the second; (3) the inert type, characerized by sluggish response to the first test meal and a marked increase during the second hour; (4) the isosecretory type, in which the gastric secretion is the same during both hours, and (5) the torpid type, in which neither the first nor second test meals excite sufficient stimulation to reveal the presence of free hydrochloric acid. A parallelism was demonstrated betwen certain pathologic states and the various types. Altshuler feels that this method possesses distinct advantages over the "single extraction method" in that it gives a true conception of the course of gastric function.

Walter M. Simpson.

Fractional Gastric Analysis with Histamine. A. F. R. Andresen, Ann. Clin. Med. **5**:472, 1926.

The use of histamine dehydrochloride hypodermically as a stimulant to gastric secretion offers a means of shortening the time required by fractional analysis.

Walter M. Simpson.

Studies in Embalming Fluids in Relation to Necropsies. John A. Kolmer and Fred Boerner, J. Lab. & Clin. Med. **11**:608, 1926.

The influence of embalming fluids on subsequent autopsies was studied with the object of overcoming the objections made by undertakers, namely, the impossibility of properly embalming the body after a postmortem examination, the increase in the cost of services, the indecent condition in which bodies are turned over to the undertaker and the difficulty in making the remains pre-

sentable. The embalming fluids commonly used were found by experiments on dogs to contain too much formalin. It is recommended that when embalming is done before necropsy the undertaker be requested to dilute his usual fluid one half for injecting the body below the head and to use the usual strength for the head. A specially prepared fluid, injected in proper amounts, was capable of preserving the bodies for weeks and even months at room temperature with remarkably slight alterations in the gross and histologic appearances of the organs. It is not difficult to meet all the legitimate objections to the necropsy raised by the undertaker either by conducting the necropsy with proper precautions or by asking the undertaker to embalm before the necropsy. If the undertaker can obtain a wide distribution of the embalming fluid throughout the capillary tree, he need not worry at all about preservation and for this purpose he may use either the usual embalming fluid diluted one-half (with full strength for the head) or one of the newer improved fluids.

THE APPLICABILITY OF COSTA'S REACTION FOR THE DIAGNOSIS OF ACTIVITY IN PULMONARY TUBERCULOSIS. E. LADECK, Beitr. z. Klin. d. Tuberk. **64**:766, 1926.

Costa's reaction (the formation of a cloud by formalin in citrated plasma) was studied on more than 200 patients. It was found to be less sensitive than the sedimentation reaction but quite applicable, particularly in cases in which it was not easy to obtain blood by puncturing the vein.

MAX PINNER.

A SIMPLE METHOD FOR BLOOD SUGAR DETERMINATION USEFUL TO THE PRACTICING PHYSICIAN. J. T. PETERS, Klin. Wchnschr. **5**:2163, 1926.

Picric acid is added to a tube containing the blood and to five control tubes containing known quantities of sugar in solution. The precipitates are filtered off and the filtrates heated on a boiling water bath for fifteen minutes. When cool the amount of sugar is directly estimated by comparison with the five controls.

J. D. WILLEMS.

A CONVENIENT METHOD FOR THE MEASUREMENT OF THE ACIDITY IN EXUDATES AND TRANSUDATES AND ITS PRACTICAL DIAGNOSTIC VALUE. C. HÄBLER, München med. Wchnschr. **73**:1970, 1926.

By determining the hydrogen ion concentration for an exudate or transudate the nature and the degree of the inflammation is established. In an acute inflammatory exudate the p_H is 6.5 or less; in a chronic exudate it is from 6.6 to 7.0; in a serous exudate it is from 6.8 to 7.2, and in a transudate it is from 7.2 to 7.4. The indicators cresol red, alpha-naphtholphthalein, phenol red, bromthymol blue, neutral red, bromcresol purple and methyl red are used.

J. D. WILLEMS.

CONCERNING THE TECHNIC OF CISTERN PUNCTURE. C. GARKAWA, Münchener. med. Wchnschr. **73**:2028, 1926.

In this method, the patient lies comfortably on his side, the needle being introduced through the membrana atlanto-occipitalis, and he is directed to "blow himself up" by taking and holding a deep breath and compressing the chest. This raises the pressure of the cerebrospinal fluid to 45 cm. of water, and it flows freely. The patient is comfortable and unalarmed, and disquieting secondary manifestations of jugular compression are avoided.

J. D. WILLEMS.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Feb. 14, 1927

LLOYD ARNOLD, *President, in the Chair*

PARASITIC NODULES RESEMBLING TUBERCULOSIS IN THE LUNGS OF SWINE. L. ENOS DAY, JOHN S. BENGSTON and H. B. RAFFENSPERGER.

Nodules caused by parasites in the lungs of swine occur often, and closely resemble miliary tubercles. So close is this resemblance that often the two varieties of nodules are distinguished macroscopically with difficulty. This distinction is important, because the final disposition of the carcass depends on which of these diseases is present. For many years it has been known that palisade worms in the lungs of certain animals cause nodules. As early as 1875, Bugnion *(Compt. rend. de la réunion de la Soc. Helvétique a Andermatt,* 1875) divided verminous pneumonia in sheep caused by *Synthetocaulus rufescens* into three types, the third form of which he designated as nodular pneumonia. The nodules range in size from that of a millet seed to that of a pea, and are either grayish yellow or dark red, according to the acuteness of the inflammatory process. This, he says, is the commonest form, and the nodules are infiltrations of the tissue caused by the ova and embryos in the alveoli. Gratia, in 1883, reported similar nodules in the lungs of swine, an observation confirmed by others.

In January, 1923, a portion of the lung of a hog with a large number of pleural nodules resembling miliary tuberculosis was received for examination from the meat inspection station of Madison, Wisconsin. Histologically, the nodules were unlike tuberculous lesions, and consisted essentially of lymphocytes arranged in small, grapelike clusters. A satisfactory interpretation was not made at that time, but later more swine lungs with similar lesions were found by inspectors in the Federal Meat Inspection Service in Chicago.

In several sections from one of these nodules were found portions of parasites containing eggs with larvae. The eggs of lung worms in swine are known to contain larvae before they are extruded by the parasite. These observations, later confirmed, established the causal agent of the lesions.

In their migration along the bronchi the lung worms sometimes penetrate the minute bronchioles, and die. They act as a foreign substance which stimulates a hyperplasia of the lymphoid tissue and the formation of the nodules.

The bronchi of the posterior parts of the lungs are more frequently infested with lung worms than those in the anterior parts, and parasitic nodules also are more frequently found in the posterior lobes, as demonstrated by the examination of 11,429 lungs of swine.

Metastrongylus elongatus occurred in the lungs of swine in relation to *Choerostrongylus pudendotectus* in the ratio of 31:7. *Choerostrongylus pudendotectus,* when present, was always associated with *Metastrongylus elongatus. Metastrongylus salmi* was not observed.

Of the twenty-three lungs with parasitic nodules containing disintegrating parasites, five contained both species, and eighteen had only *Metastrongylus*

elongatus in the bronchioles. Of the forty-six lungs with nodules in which parasites were not demonstrated, thirty-eight contained *Metastrongylus elongatus* only, and eight contained both parasites. Of the fifty-five lungs without nodules, forty-one contained *Metastrongylus elongatus* only, and fourteen contained both parasites.

It seems, then, that *Metastrongylus elongatus* causes the nodules described in the lungs of swine, possibly also *Choerostrongylus pudendotectus,* but since lungs with the latter parasitic infestation alone were not found, definite conclusions may not be reached from the results of our investigations.

The complete report will be published in the *Journal of the American Veterinary Medical Association* for 1927.

A Large Hyperostosis of the Cranium Due to Arachnoid Fibroblastoma, Mallory (So-Called Dural Endothelioma). S. M. Crowe (John Jay Borland Fellow in Medicine) and C. K. Jones. (From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago).

Hyperostosis of the cranium with endothelioma of the dura has been reviewed by Cushing (*Arch. Neurol. & Psychiat.* **8**:139 [Aug.] 1922; *Brain* **45**: 282, 1922), Penfield (*Neurol. & Psychopath.* **4**:27, 1923; *Surg. Gynec. & Obst.* **36**:657, 1923) and others. It is not an unusual condition, although according to Cushing, its occurrence in the first two decades of life is rare. His statistics indicate that these tumors, which he chooses to call meningiomas, occur in a ratio of about 1:4 to the gliomas. These meningiomas comprise about 10 per cent of the verified tumors of the brain and in about 25 per cent of them there is an accompanying localized thickening of the cranial bone. More than once the exostosis has been considered the primary new growth and has been removed, the symptoms returning after a time, as reported by Spiller (*J. A. M. A.* **49**:2059 [Dec. 21] 1907). The bony swelling has recurred also, as reported by Rand (*Arch. Surg.* **6**:573 [March] 1923), and although it was removed a second time, it has reappeared, and the underlying tumor has been removed only at the third operation.

J. J., a schoolboy, aged 16, was admitted to St. Luke's Hospital as a patient of C. K. Jones and E. W. Ryerson on March 3, 1926, with a bony tumor of the forehead. Eleven years before he had fallen down a short cellar stairway, striking his forehead on the cement floor. Two weeks later a small, smooth lump was noticed, and it was considered by a physician to be a hematoma. For three years, there was no appreciable change in the size of the lump, and then when the boy was 8 years old it started to grow, painlessly and symmetrically. During the last three years there had been little change in its size, except that the mother thought that there had been definite growth for several months before he entered the hospital. The boy had had repeated epileptiform attacks since the age of 10. The first seizures, occurring during a period of two days as repeated spastic convulsions, were considered due to dietary indiscretions. The second attack, a year later, was characterized by loss of consciousness and falling to the floor, as was the third a month later. After three years, at the age of 15, the boy had three short convulsions in one week, the first following a heavy meal. One year later, in January, 1926, he had two short convulsions, one lasting three minutes, the other only a minute or two. Since then the mother had noticed that her son on two or three occasions apparently lost consciousness for a moment or so. He did not fall, but seemed "absent." A playmate had noticed the same thing. The patient was unconscious during all of the attacks, and they occurred without warning. In each

instance there was rigidity during the seizure and severe headache following it, relieved according to the mother, by a dose of castor oil. There was a history of considerable gastro-intestinal disturbance from infancy through childhood, and of asthmatic attacks since the age of 8. Besides the usual diseases of childhood, the patient had had bronchopneumonia, pleurisy and erysipelas.

During the examination at the hospital little was found except the swelling of the forehead. Results of a previous roentgen-ray examination were reported by Hollis E. Potter as follows: "There is an enormous laying down of new bone, suggestive of an osteoma, apparently not penetrating beneath the lower table." Neurologic examination by G. W. Hall disclosed no organic disturbance of the central nervous system. The patient was alert, and there was no mental deterioration.

At the operation, noted by an intern "to be one of mental therapeutics and cosmetic," an "osteoma of the frontal bone" was sawed off. The tumor was symmetrical with respect to the midline of the skull, and the periosteal covering was adherent to it and about 3/8 of an inch (0.96 cm.) thick. Results of the roentgen-ray examination ten days after the operation were reported by E. L. Jenkinson as follows: "The large osteoma involving the frontal bone has been removed. The internal table is intact except for a small area about 1½ inches (3.77 cm.) above the glabella."

Eleven months after the operation the boy is apparently well, is an honor student in high school, and is a member of the school swimming team. He has been taking phenobarbital, supposedly, every day since the operation, and he has not had any more convulsions. In recent roentgenograms there is no noteworthy change in the shadows of the cranial bone. Vision and eyegrounds are normal.

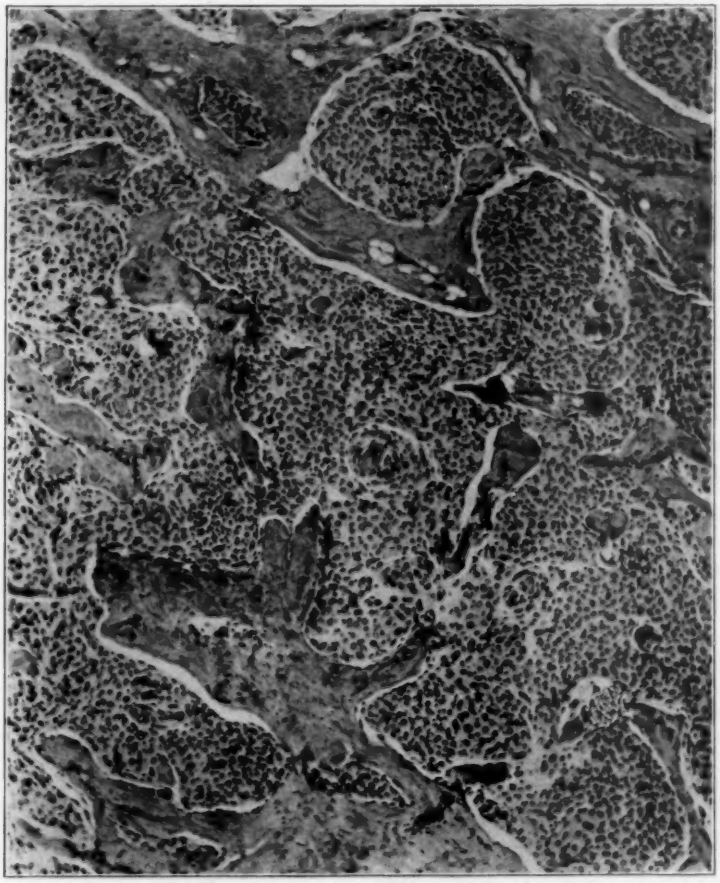
The tissue removed at operation was examined by Edwin F. Hirsch, who reported the following observations: The three pieces of compact bone were 9 by 3.3 cm., 9 by 3.5 cm., and 9 by 4.5 by 2 cm. They seemed to have been cut from a roughly spherical mass. On the surfaces that had been sawed there was hard, bony, tissue-like cortex; the parts on the outside were porous, and some were covered with a little closely adherent fibrous tissue. With these was a roughly wedge-shaped piece of fibrous tissue 9.5 by 3 by 1 cm. The three pieces of bone together weighed 156 Gm.

Sections of the fibrous tissue (the periosteal covering) contained dense masses of hyaline fibrous tissue and collagen. Between the fibrous septums were masses of large polygonal cells, which in the hematoxylin-eosin stain had a faint purple cytoplasm and a vesicular round nucleus. These in places were arranged concentrically, some around small blood vessels. In sections of the bone there were similar masses of these cells in the large marrow spaces. With special stains, such as phosphotungstic acid-hematoxylin, Weigert's elastic tissue and aniline blue, the specific staining qualities of the collagen and elastic fibers were demonstrated. These staining reactions and the histology permitted the diagnosis of a so-called "dural fibroblastoma."

Comment.—According to Cushing, the view that a "dural fibroblastoma" arises from the arachnoid, was first expressed by John Cleland, of Glasgow, in 1864, and similar opinions were later given by C. Robin of France (1869), by Schmidt (1902) and by Weed and Cushing (1915). Mallory (*J. M. Research* **41**:349, 1920) published a histologic study with the statement that there is no dural endothelium, and that the tumors commonly considered as arising from such a structure in reality develop from the growing cells of the arachnoid. Two years later, Cushing discussed the origin from the arachnoid, the favored

places of occurrence and the factors in the development. As factors he considers age, congenital predisposition, trauma and the physiologic activity of the cells of the arachnoid concerned. He considers the relation to trauma close and more than coincidence.

The tumor is not known to metastasize (Towne: *Ann. Surg.* **83**:321, 1926), although it may invade the dural sinuses and may extend through the cranium and into the scalp and temporal muscles. It may displace and compress brain



Photomicrograph illustrating structure of a tumor; × 75.

tissue, but according to Mallory, "it cannot pass through the arachnoid from which it has risen and invade the brain."

Microscopically, Mallory describes the arachnoid fibroblastoma as composed of cells that are usually large and more or less flattened, but sometimes spindle-shaped, often having a marked tendency to wrap themselves about each other, around strands of connective tissue or around blood vessels, forming concentrically arranged masses of cells or whorls of various sizes. The cells may be arranged in a palisade effect. The whorls may be fibrous. With slow growth fibroglia, collagen and elastic fibrils may be formed.

The manner of growth of the hyperostosis has been studied by Phemister (*Arch. Surg.* **6**:554 [March] 1923). He believes that the tumor stimulates the production of new bone which is itself not tumorous. The pad of tumor tissue between the hyperostosis and the scalp has been described by Penfield.

The tumor may exist without symptoms, the manifestations depending on the size and location of the intracranial growth. The bony swelling, when present, may or may not be painful or tender. Convulsions, either generalized or localized to one part of the body, have been reported repeatedly. Headache is probably even more frequent, and in the cases reported by Penfield it was of a stabbing or neuralgic character, rather than of the increased intracranial pressure type. Hemiplegia, eye changes and mental disturbances are less commonly observed.

It is Cushing's opinion that "unquestionably many of these lesions are never recognized during life and even if a diagnosis of tumor suspect be made, localization may be extremely difficult in the absence of hyperostosis, palpable or shown by the roentgen-ray." Sosman and Putnam (*Am. J. Roentgenol.* **13**:1, 1925), reviewing the roentgenograms of ninety-five verified intracranial meningiomas, found in nearly half of them recognizable changes characteristic of the tumor, but in discussing the differential diagnosis they state that it may not be possible to distinguish between osteoma and the tumor except by operation.

The treatment of patients with arachnoid fibroblastoma is surgical. As stated by Cushing, the tumor may increase in size without giving evidence of its growth, so that the operation for its removal may be most formidable. Cushing, Penfield and others have called attention to the fact that the tumor apparently does not recur locally when a little is left, either in the muscles of the scalp or at the attachment to the dura. Both report the cases of patients who were well twelve years after operation. Sosman and Putnam, however, mention five patients operated on a second time, one as long as nine years later, for recurrence of the tumor.

Microscopic Changes in Sickle Cell Anemia. I. Pilot.

My interest in sickle cell anemia (Herrick) was aroused by recognizing the disorder in tissues of a young negro in whom the disease was not recognized clinically. The tissue changes are so definite that this peculiar anemia may be identified without difficulty in microscopic preparations. The recorded descriptions of tissue changes are limited, there being only four based on examination of tissues at autopsy. These reports were made by Huck, Graham and Sydenstricker. I shall mention the essential features of the disease in another patient.

A negro, aged 16, entered the Cook County Hospital complaining of pain in the ankles and knees, malaise and anorexia of one week's duration. He said that about ten days before he had had a "cold," and three days later he had felt pain in the left ankle. Pains in the knees and in the lumbar region appeared on the following day. Profuse sweats occurred several times. Similar attacks of pain and sweats occurred two weeks prior to the present attack, and similar attacks had been noted before. He had had a chancre four months before and had received six "injections."

Physically, the boy appeared ill; his temperature was 101.8 F., his pulse rate, 112, and his respirations, 24 per minute. The head presented patchy alopecia and the skin contained macular patches, especially on the forehead, the palms and extremities. The sclerae were markedly icteric. The lips were

fissured, the teeth were good, and the tonsils were large. The lungs were resonant; the heart had a systolic blow at the apex. The abdomen was tympanitic, the liver extending two fingerbreadths below the costal arch. There was a healing chancre on the shaft of the penis, a marked tenderness about the knee and ankle, but no swelling or edema. All the lymph nodes were moderately enlarged and hard. A clinical diagnosis of secondary syphilis and icterus due to arsenic therapy was made. The patient's temperature rose to 105 F.; he became more toxic, and died within forty hours after admission. The urine contained albumin. The Wassermann reaction was reported 4 plus.

The anatomic diagnosis showed: macular rash of the skin, icterus, bilateral fibrous pleuritis, caseated and calcified tuberculosis of the parabronchial lymph nodes, petechial hemorrhages of the epicardium, slight sclerosis and bile staining of the aorta. The thymus was 7 cm. at the base; the spleen weighed 150 Gm., and the capsule was thickened and wrinkled. On surfaces made by cutting there was a marked increase of the connective tissue, with peculiar raised gelatinous regions that stood out prominently. The liver weighed 2,800 Gm. It was soft, light brown, and the markings were obscured. The kidneys were enlarged, the left weighing 270 Gm. and the right 250 Gm. The capsule was stripped with difficulty, and depressions were left on the surface. The markings were fairly clear. The suprarenals were normal in size and contained little lipoid in the cortex. The bone marrow was red in places. The pancreas, prostate and urinary bladder were unchanged.

The spleen was markedly hyperemic and hemorrhagic. The trabeculae were thickened and contained large quantities of brown and yellow pigment, most of which gave a positive iron reaction. Often there were associated calcium deposits. There were only small islands of lymphoid tissue. About the pigment and calcium deposits was an occasional foreign body giant cell. The pulp was densely packed with bundles of sickle-shaped red blood cells. The sinuses were lined by endothelial cells without phagocytosis. There were many sickle-shaped red cells within the sinuses, together with a few macrophages containing iron pigment and phagocytosed red cells.

The sinuses of the liver were distended with round and sickle-shaped erythrocytes. There were many coiled masses of sickle cells which were large Kupffer cells crowded with phagocytosed red cells. The cords of the liver cells were narrow and contained fat, but there was no iron-containing pigment. The reticulum was distinctly increased, and the capillaries slightly thickened.

The vessels of the kidney were engorged, and the capillaries of the glomeruli were prominent. Bowman's space was narrow. The epithelium of the convoluted and collecting tubules contained large deposits of iron-containing pigment. The interstitial tissue was slightly increased and infiltrated with a few round cells.

The lymph nodes had dilated sinuses in the medulla and poorly developed follicles in the cortex. The capsule and the trabeculae were thickened. The sinuses contained many phagocytic endothelial cells with engulfed round and sickle-shaped red cells. A small amount of iron-containing pigment was present under the capsule.

The bone marrow had many regions of erythropoesis and granulopoesis. The sinuses were filled with nucleated erythrocytes and occasional nucleated sickle cells. There were numerous sickle cells, together with various types of immature and mature myelocytes. Megokaryocytes were abundant. Numerous macrophages packed with phagocytosed red cells, many of the sickle cell type were present in the sinuses.

In the myocardium there was a slight edema, fragmentation of the fibers, dilated vessels and no pigment. The thymus did not contain any noteworthy changes. The lungs were unchanged except for engorged capillaries, but there was no phagocytosis by the endothelium.

The distinctive changes noted in the examination of these tissues were the marked distention of the vessels with many sickle cells, the marked phagocytosis in the liver, lymph gland and bone marrow and the large deposits of iron-containing pigment in the spleen and kidneys. Hemorrhages had occurred frequently in the spleen, and these tissues especially were changed. The histologic changes observed in the tissues mentioned corresponded closely with those observed by R. H. Jaffé in the tissues of two other patients in whom sickle cell anemia was recognized clinically.

DISCUSSION

R. H. JAFFÉ.—In sickle cell anemia the erythroblasts and normoblasts in the bone marrow appear morphologically normal. The transformation of the erythrocytes to sickle cells takes place in the organs of the reticulo-endothelial system, especially in the spleen. The sinuses of the spleen contain only sickle cells, while in the peripheral blood, from 4 to 40 per cent of the red cells are disfigured. The sickle cells are phagocytosed by the Kupffer cells of the liver and by the reticulo-endothelial cells of the abdominal lymph nodes. Phagocytosis practically does not occur in the spleen.

The anatomic changes in sickle cell anemia resemble those found in hemolytic jaundice.

OSTEITIS DEFORMANS (PAGET'S OSTEITIS, OSTEO-DYSTROPHIA FIBROSA SENILIS [CHRISTELLER-FRANGENHEIM]). R. H. JAFFÉ.

The clinical history of this patient is interesting because of the connection between trauma and the onset of the disease. A woman, aged 83, fell on her right knee twenty years ago while alighting from a street car. Since that time she had noticed a swelling of the injured knee, which gradually extended over the right thigh. Later the tibia and the left lower extremity became affected. The patient was bedridden for fifteen years. In the last five years the upper arms started to swell. She died of angina pectoris.

Autopsy demonstrated an enormous deformity of the lower extremities. The circumference of the right thigh was 52 cm., that of the left, 87 cm. Both femurs resembled a watermelon in size and shape. The weight of the right femur was 6 Kg. The cross diameter in the middle of the diaphysis was 16 cm. The histologic changes were typical of osteitis fibrosa. There was a dense network of osteoid tissue trabecula with little calcification and many osteoclasts. The bone marrow in the peripheral parts of the diaphysis consisted of a loose fibrillar connective tissue with accumulations of round cells and many mast cells. The hyperemia of the marrow, a characteristic which has been emphasized by Pommer and F. J. Lang, was marked. In the center of the diaphysis and in the epiphysis fatty marrow was found. It contained much myeloid tissue, the myeloid metaplasia apparently being due to infections that had started from ulcerations of the skin about the deformed bones.

Besides the femurs, both tibias and the lower end of each humerus were involved in the process.

The parathyroids microscopically had the structure found in aged persons. There was no hyperplasia. Calcium metastases were observed in the convoluted tubules of the kidney and in the lymph vessels about the inguinal lymph glands.

Fig. 1.—Roentgenogram of the right femur.

Fig. 2.—Transverse section of the right femur.

The following anatomic changes were found in the other organs: scirrhus carcinoma of the right breast, bilateral hemorrhagic bronchopneumonia, marked sclerosis of the coronary arteries, chronic fibrous myocarditis, atrophic cirrhosis of the liver, chronic cholecystitis, cholelithiasis and chronic diffuse nephritis—primary contracted kidneys, right nephrolithiasis and marked atheromatous sclerosis of the abdominal portion of the aorta.

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 10, 1927

EUGENE L. OPIE, *Presiding*

MASSIVE FALSE ANEURYSM OF THE ABDOMINAL AORTA. J. M. HAYMAN, JR. (From the service of Arthur Newlin at the Pennsylvania Hospital.)

A negro man, aged 53, was first admitted to the hospital on July 23, 1925, with a history of having had a pulsating abdominal mass since 1918. At that time, he received antisyphilitic treatment, and the mass did not increase appreciably until 1924. There was little change after he came under observation until September, 1926, after which the tumor grew rapidly, rupturing externally in the left iliac region on Feb. 12, 1927. Blood Wassermann reactions were repeatedly negative. The aorta was somewhat dilated throughout its course; above the aortic valve the intima showed slight longitudinal wrinkling and some hyalinization, giving the picture of syphilitic aortitis. Five centimeters distal to the origin of the renal arteries there was a sudden sharp saccular dilatation about 12 cm. in diameter, the wall of which contained many calcified plaques. From the left side of this saccular enlargement, an orifice about 4 cm. in diameter communicated with a huge, firm, thrombus-filled, retroperitoneal mass, 40 by 23 by 18 cm., whose walls were fused with the surrounding tissue. The right common iliac artery arose abruptly from the lower right posterior aspect of the smaller sac; the left common iliac artery rose from the left inferior aspect, just distal and slightly anterior to the orifice communicating with the false aneurysm. The thrombus-filled mass, together with the heart and aorta, weighed 5,500 Gm. The bodies of the fourth and fifth lumbar vertebrae and the wing of the left ileum had been eroded. The heart was rather small, and showed evidence of syphilitic vascular disease with associated scarring in the myocardium.

The case was of interest because of the rather unusual location of the aneurysm, its long duration and the massive proportions reached before death. The negative Wassermann reactions were confusing, but the history of antisyphilitic treatment may have had some bearing.

ACUTE HEMORRHAGIC PANCREATITIS IN A DIABETIC CHILD. EDWARD S. DILLON.

A boy, aged 10, was admitted to the Pennsylvania Hospital in the service of George W. Norris on Nov. 13, 1926, and died on Nov. 16, 1926.

His family and past histories were not noteworthy. Two years previously he had begun to lose weight, and at the Children's Hospital his parents were told that he had diabetes. The dietary instructions were not followed, and his mother said that he ate twice as much as any of her other children. He

continued in school, and was able to be up until two weeks before admission to the hospital, when increasing weakness, together with marked polydipsia, polyuria and polyphagia forced him to go to bed. On the 13th, at 5 a. m., he was suddenly seized with a severe pain in the back and in both axillae. At 11 a. m. he became stuporous, and at 2 p. m. he was brought to the hospital.

The outstanding features observed on physical examination were that the patient was undernourished and comatose, had an odor of acetone on his breath and had soft eyeballs; that the veins over his thorax and abdomen were prominent; that there were a few râles in his right axilla; that his abdomen was much distended and tympanitic and did not show rigidity or evidence of fluid, and there was only slight peristalsis. He had 4.7 per cent of sugar in his urine; his blood sugar content was 455 mg. per hundred cubic centimeters of blood; the temperature was 98.4 F.; the pulse rate was 132, and the respiration was 30.

During the afternoon and evening of November 13 he was given 80 units of insulin. At 10 a. m. on November 14, his blood sugar content was 98, p_H 7.2. He obeyed orders, but did not speak. However, his abdomen was more distended, and this condition became steadily worse. On the afternoon of the 14th he began to have spastic contractions of his arms and legs, and the blood sugar content was found to be 45. These continued even after glucose had been administered intravenously, though less severely, the blood sugar content being 308. Except for a brief time on the 14th, he remained comatose, and he died at 2 p. m. on the 16th. His temperature ranged from 98 to 101 F. until 5 a. m. on the 16th, when it went to 107 F. His white blood cells were 30,000 on admission, 9,200 on the 14th, and twice later 4,900. During the last twenty-four hours there was complete anuria.

At autopsy the peritoneal cavity was found to contain about 200 cc. of dull, pale yellow, cloudy fluid, which proved to be sterile. In the mesentery and tissues around the pancreas there was an extensive, rather diffuse, pale yellow, patchy appearance. These areas were soft and somewhat doughy in consistency. The pancreas was surrounded by a large amount of adherent tissue, which showed the areas mentioned. The organ was quite firm in consistency. On section it showed heavy fibrous trabeculations and a firm fibrous capsule in which the yellow areas were seen in patchy distribution. In the tail of the pancreas there was an area near the inferior border about 1 cm. in diameter, which had the appearance of a sharply circumscribed clot of blood. Examination of the ducts failed to show any evidence of obstruction. Microscopically, there was extensive and almost universal necrosis of the stroma, with extensive infiltration of polymorphonuclear leukocytes. Necrosis in the parenchyma was limited to small isolated areas, and the islets of Langerhans did not show any histologic change.

Hodgkin's Granuloma in the Liver. Baldwin Lucke.

The essential dissimilarity between lymphogranulomatous tumors and true metastatic neoplasms is illustrated by the case reported.

A white man, aged 46, had suffered for some years from Hodgkin's disease involving primarily the retroperitoneal and abdominal lymph nodes; later the superficial lymph nodes were also affected (Boles, R. S.: M. Clin. N. Amer. **10**:313 [Sept.] 1926).

At autopsy the liver was found to be moderately enlarged (2,290 Gm.). Beneath its capsule, as well as throughout the interior, there were a number of whitish, round or roughly quadrangular tumors, the largest of which

measured about 4 cm. in diameter. In the cut surfaces of these tumors distinct bands of liver tissue were grossly noted.

Histologic examination showed typical nonfibrosed Hodgkin's lymphogranulomas; the predominating cells were mononuclear and multinuclear giant cells and endothelial elements; but the usual confused mixture of lymphocytes, leukocytes and eosinophils existed as well.

Within the tumors there were many patches of well preserved liver tissue, some continuous with the hepatic tissue surrounding the lesions and other patches forming separate islets. In the completely granulomatous areas the reticular framework was still largely preserved, and the sinusoids, as well as the space formerly occupied by the hepatic cells, were occupied by the cells of the granulomatous tumor.

The reticulo-endothelial cells of the sinusoids in the preserved liver tissue at the edge of the growth, as well as in the patches enveloped by the growth, showed distinct enlargement. Many sinusoids contained mononuclear and multinuclear giant cells identical with those of the tumor. There were all gradations between enlarged reticulo-endothelial cells still forming a lining and detached giant cells, suggesting the close relation between the native reticulo-endothelial cells and the predominating elements of the granuloma.

The Hodgkin's granuloma of the liver reported differs from true metastatic neoplasms by its intimate relation with the hepatic tissue, and by the apparent derivation of its predominating cells from the reticulo-endothelial elements of this organ.

CONSIDERATION OF HOST SUSCEPTIBILITY AND PNEUMOCOCCUS TYPES IN LOBAR PNEUMONIA. F. D. W. LUKENS.

I have reviewed fifty-five cases of lobar pneumonia, under observation at the Pennsylvania Hospital during 1925, in which serum treatment was not used and I have summarized in statistical form the relation of the type of infecting organism to age, sex, season and the complications of the disease. Although I can draw no conclusions from such a small series of cases, I am left with certain impressions. Type I is a disease of early life, especially frequent in men and producing by far the greatest number of complications. Type II shows somewhat the same picture, although these characteristics are less obvious. The aged and women are more subject to type III and to nonspecific type IV infections. Although the part played by exposure to virulent pneumococci, or the so-called contagion factor, is an uncontrolled variable in this series, I have felt that the differences in incidence are due primarily to the factors governing the susceptibility of the host.

THE PNEUMOCOCCUS COLONY. JOHN R. PAUL.

Recent advances in knowledge have shown that, as in the case with certain other species of bacteria, avirulent variant strains or so-called "rough" strains of the pneumococcus may be produced under certain environmental conditions from the virulent or "smooth" parent strains. The terms "rough" and "smooth" are derived from the characteristic type of colony which is formed by each strain, although other recognized differences in virulence, antigenic properties, capsule formation, and other properties, exist between the two strains. I have recently had occasion to make a comparative study of "smooth" and "rough" pneumococcus colonies, for, although descriptions of the former are well recognized, the latter or "rough" colonies have been described only in somewhat general terms.

Methods.—All studies of colonies were made under the low power objective of the microscope, with reflected light from the surface of a tilted blood agar plate. Discrete colonies occurring in twenty-four hour cultures on fresh rabbits' blood agar (p_H 7.6) were chosen as a standard. Freshly isolated strains of type specific pneumococci were chosen for the "smooth" colonies. The "rough" strains were obtained from the Rockefeller Institute for Medical Research, through the kindness of Dr. O. T. Avery.

"Smooth" Colonies.—The characteristic features of "smooth" pneumococcus colonies have long been recognized, and were accurately described by Buerger more than twenty years ago. He emphasized their relative variability in size and shape, but the most typical discrete colonies occurring in luxuriant growth were described as being circular, disk-like and flattened, with a glassy surface and often a slightly depressed center. These forms were designated as "ring types." Other descriptions may be found in most of the recognized textbooks on bacteriology. Recently, Atkin has made a number of interesting observations on the appearances of changes in smooth colonies in old cultures.

Typical smooth colonies such as the one described may, of course be subject to many environmental alterations. I have studied the effects of crowding, age, drying, diminution of nutrient substances and variations of the p_H of the mediums and I have found that in old cultures (that is from 48 to 96 hours old) and in cultures in which the blood has been reduced below 5 per cent, "pseudo-rough" colonies will frequently be produced. The change is transient, however, and a strain thus treated for only a few generations does not lose its type specificity, and quickly regains its ability to produce "smooth" colonies on transfer to suitable mediums.

"Rough" Colonies.—Again there is considerable variation in size and shape of the typical colonies. They seem to resemble the colonies of certain strains of streptococci more than they do "smooth" pneumococci. As a rule they are smaller than the smooth variety, and are more likely to be elevated and dome-shaped than flat and disk-shaped. They are nearly always circular and show a slight granularity or roughening of the surface, which is more pronounced in the 48 hour and 72 hour cultures. With age they show a tendency to produce a central elevation rather than the central depression of the "ring type" of colony. If crowded together, individual colonies become diminished in size, but do not show the marked tendency to coalesce which is exhibited by the smooth forms. Drying and diminution of the blood in the mediums accentuate the roughness of the surface.

AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

Twenty-Seventh Annual Meeting, Rochester, N. Y., April 15 and 16, 1927

HANS ZINSSER, *President;* HOWARD T. KARSNER, *Secretary*

Special Report

The first session was given over to a joint meeting with the American Association of Immunologists. At the second session G. R. Callender and J. F. Coupal gave the first annual report of the registry of tumors of the lymphatic system.

James Ewing urged the bacteriologic study of all such tumors. A. S. Warthin considered infection without significance in lymphosarcoma, Hodgkin's disease, leukemia, etc. Hans Zinsser doubted the infectious nature of Hodgkin's disease. Herbert Fox could not produce Hodgkin's disease in monkeys by injecting the organism of Grumbach. Herbert Fox discussed the relation to certain lymph node diseases of polymorphonuclear neutrophils and their reaction to the roentgen ray. Harry T. Marshall and Katherine Woodward described acute leukemia in a child with myeloid centers outside the marrow, particularly in the kidney and dura. Oscar T. Schultz reported a diffuse lymphoma of the mesentery associated with carcinoma of the colon; Maurice N. Richter, a generalized reticular cell sarcoma of lymph nodes with lymphatic leukemia, and George Baehr and Nathan Rosenthal, several cases of malignant hyperplasia of the spleen and lymph nodes. F. B. Mallory and Frederic C. Parker, Jr., stated that so-called reticulin is not a distinct substance but corresponds presumably to collagen. Carl V. Weller described an umbilical growth of endometrial tissue that swelled up and discharged blood at the menstrual periods. Lawrence W. Smith described three tumors about the knee of synovial cells — synovioma. William E. Jacobs reported a mediastinal dermoid with meningeal metastases, and Wilder Penfield classified encepsulated tumors of the nervous system on the basis of cell types.

At the third session V. C. Jacobsen and K. C. Waddell reported that the high voltage cathode rays exercise an extremely destructive effect on living tissues even on exposures of less than one second. Gordon M. Kline isolated bacteriophage from eleven to fourteen stock cultures. J. Bronfenbrenner claimed that bacteriophage is particulate because in suspension it passes through a permeable membrane at first and then stops doing so, indicating the presence of larger particles or aggregations of particles. J. Bronfenbrenner, R. S. Muckenfuss and D. M. Hetler illustrated by moving photomicrographs lysis of bacteria by phage. Just before lysis the bacteria enlarge with increase in viscosity. Edward Francis and G. N. Callender described the lesions of tularemia in man; in both nodular and radiating lesions, round cells are the conspicuous elements. Injecting India ink and tubercle bacilli, Samuel R. Haythorn found that the bacilli are carried by large mononuclear cells. According to E. R. Medlar, demonstration of the causative agent may be necessary in order to distinguish between blastomycosis and tuberculosis of the lungs. G. Y. Rusk detailed four cases of meningitis caused by *Coccidioides immitis*. In West African yellow fever Oskar Klotz and Winnifred Simpson found the spleen not enlarged, the malpighian body small with central degeneration and accumulation of endothelial cells at the borders. James Davis analyzed eighteen instances of congenital cystic kidneys. H. E. Robertson reported hypoglycemia in a man with carcinoma of the islands of Langerhans.

At the fourth and last session Maude E. Abbott described an example of the adult type of coarctation of the aorta with obliteration of the descending arch. J. S. McCartney found in 9,000 autopsies 73 instances of pulmonary embolism, which he grouped as traumatic 15, operative 30, traumatic and operative 9, puerperal 3 and medical 16. William Boyd in a case of pulmonary carcinoma found sclerosis of the pulmonary artery. Otto Saphir and R. W. Scott discussed the frequent gluing together of the lateral edges of the aortic valves in syphilitic aortitis. B. J. Clawson, from a study of 126 cases of syphilitic aortitis stressed the thickening of the free margins of the aortic valves and the narrowing of the coronaries in some cases. In 400 cases of primary hypertension E. T. Bell found sclerosis of arterioles much more significant than of the larger

arteries. Leone McGregor takes the blood pressure in rabbits by placing the sphygmomanometer cuff around the abdomen and the stethoscope partly below the lower edge and over the femoral vessels. A. H. Pedersen produced hypertension in rabbits by constricting the kidneys with an aluminum band. LeRoy U. Gardner and David T. Smith reported that the pulmonary alveoli do not have an epithelial lining and that the alveolar phagocytes arise from connective tissue. Alfred Plaut described an instance of the rare occurrence of secretory glands in the vaginal wall (diffuse adenosis).

Book Reviews

IMMUNITY IN SYPHILIS. ALAN M. CHESNEY, Johns Hopkins Medical School, Baltimore. Price, $2.50. Pp. 85. Baltimore: Williams and Wilkins Company, 1927.

The author deals extensively with the behavior of syphilitic animals toward reinfection with syphilis, and it is largely in connection with this problem that the monograph represents an advance over earlier summaries. This matter is of practical importance, since chancre formation on reinoculation of previously infected and treated animals has been a common criterion for testing the efficacy of various drugs used in the treatment of syphilis. This procedure is founded on Neisser's conception that resistance to reinfection is dependent on existing infection and that the resistance disappears with cure.

Neisser's experimental procedure is criticized, and his contention is challenged by the following experimental data:

1. In infected, treated and reinoculated animals the percentage of reinfection varies, depending on the time that treatment was instituted with reference to the primary infection. The earlier treatment is begun, the higher is the percentage of reinfections, while after the ninetieth day reinfection is rare. Animals treated either early or late can, however, be rendered incapable of transferring infection to normal animals through transfer of tissue (lymph nodes, spleen, heart, liver, bone marrow or brain). The author believes that these facts are best explained by the development of an active immunity, which, when once established, may persist in the absence of infection. Clinical experience is not in conflict with this conception.

2. Reinfection as determined by transfer of lymph nodes and the reappearance of a positive Wassermann reaction may occur without the development of a lesion at the portal of entry.

3. A higher percentage of reinfections is obtained when a heterologous strain is used for reinoculation.

4. A notably higher proportion of reinfections develops when reinoculation is made on a granulating surface (rabbit's back) than when the usual methods are employed.

Other phases of syphilitic immunity in man and in experimental animals are also considered, and the book will be of special interest to all students of immunity as it relates to syphilis.

PNEUMOCONIOSIS (SILICOSIS): A ROENTGENOLOGICAL STUDY WITH NOTES ON PATHOLOGY. By HENRY K. PANCOAST, M.D., Professor of Roentgenology, University of Pennsylvania, Philadelphia, and EUGENE P. PENDERGRASS, M.D., Associate in Roentgenology, University of Pennsylvania, Philadelphia. Cloth. Price $4. Pp . 186. New York: Paul B. Hoeber, 1926.

This monograph brings a timely and welcome discussion of pneumoconiosis which has not been investigated as systematically in America as elsewhere. The various dusts causing pathologic changes in the lungs and the methods of prevention, including the respective state laws in a number of countries, are discussed. There is a chapter on pathologic anatomy, bringing out the essential points of silicosis as observed on the postmortem table and in the microscopic slide, followed by

the best part of the book, the roentgenologic study of pneumoconiosis. Twenty-three roentgenograms illustrate the material in the text; they are well reproduced, and their study is facilitated by brief but complete legends. Coincident tuberculosis and the relative hazard of pneumoconiosis in a number of occupations based on the authors' material complete the book. An international bibliography of seventy-three selected references will be of help to the reader looking for further information on the subject. Although the major part of the monograph is devoted to the roentgenologic side of the problem, it should prove of interest to the pathologist, not only because the roentgen-ray examination is the most important agent in studying this condition in the living, but also because correct interpretation of these roentgenologic observations will depend on the correlation of roentgenology and pathologic anatomy.

A Survey of American Chemistry, Vol. 1, July 1, 1925 to July 1, 1926. Price $2. Pp. 257. New York: The Chemical Catalog Company, 1927.

The Division of Chemistry and Chemical Technology of the National Research Council has initiated this report as the first of a series of annual statements of the advances made in research in this country during the year covered, together with the presentation of lists of problems needing solution by chemists. Most of the topics covered deal chiefly with problems in pure and applied chemistry not directly related to medicine. Of medical interest are particularly the chapters on Pharmaceutical Chemistry by Francis O. Taylor, Organic Medicinals by Marston T. Bogart, Biochemistry by Donald D. Van Slyke, Water and Sewage by Edward Bartow, and Proteins and Nucleic Acids by Phoebus A. Levene. The several authors have done their work well. Their brief presentation of so many topics under active investigation makes interesting reading, and should serve the purpose of stimulating further research. The limitation of the discussions, however, to a recital of the work done in one country makes the compilation of limited value and leaves the reader with a dissatisfied recognition of incompleteness, especially when subjects such as the structure of proteins, in which most of the work has been done in other lands, are under consideration.

Books Received

GLYCOGENE ADRENALINE ET INSULINE. By M. Jacot. Pp. 212. Price, 35 francs. Paris: Masson et Cie, 1927.

PRAKTIKUM DER KLINISCHEN-CHEMISCHEN, MIKROSKOPISCHEN UND BAKTERIOLOGISCHEN UNTERSUCHUNGSMETHODEN. Von San.-Rat Dr. M. Klopstock und Dr. A. Kowarski in Berlin. Achte, umgearbeitete und vermehrte Auflage. Mit 48 Abbildungen im text und 25 farbigen tafeln. Pp. 519. Price, 13.50 marks. Berlin: Urban & Schwarzenberg, 1927.

DIE PATHOGENEN MIKROORGANISMEN DES AUGES. Von Prof. Dr. F. C. Herrenschwand, Innsbruck. Mitt 17 Abbildungen im text, 12 farbigen tafeln und einer tabelle. Berlin: Urban & Schwarzenberg, 1927.

HANDBOOK OF SCIENTIFIC AND TECHNICAL SOCIETIES AND INSTITUTIONS OF THE U. S. AND CANADA. American Section compiled by Clarence J. West and Callie Hull for the Research Information Service, National Research Council, United States; Canadian Section compiled by National Research Council, Canada. Pp. 304. Price (paper), $3. Washington, D. C.: The National Research Council of the National Academy of Science, 1927.

STUDIES ON CLONORCHIS SINENSIS (COBBOLD). By Ernest Carroll Faust, M.A., Ph.D., and Oo-Keh Khaw, M.B., Ch.B., D.P.H., D.T.M. Assisted by Yao Ke-Fang, M.D., and Chao Yung-An. With a Consideration of the Molluscan Hosts of Clonorchis Sinensis (Cobbold) in Japan, China and Southeastern Asia and Other Species of Molluscs Closely Related to Them. By Bryant Walker, Sc.D. Illustrated with 14 plates and 33 text figures. Pp. 284. Baltimore: The American Journal of Hygiene Monographic Series, no. 8, 1927.

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